First-in-human phase I trial of anti-Hepatocyte Growth Factor (HGF) antibody (YYB101) in refractory solid tumor patients: Safety and Efficacy analysis

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Introduction

• Hepatocyte growth factor (HGF) and Mesenchymal epithelial transition factor (cMET) were reported to be excessively expressed in various human tumor tissues including the brain, liver, prostate, colon, breast, and skin.

• YYB101 is a neutralizing antibody that specifically binds to human hepatocyte growth factor (HGF) to inhibit its activity. By binding to HGF, YYB101 blocks the HGF/cMET signaling pathway to inhibit tumor growth, migration, and infiltration. This mechanism was confirmed by in vitro studies, showing that the antibody effectively inhibited the phosphorylation of ERK factors downstream of HGF/cMET.

• Herein, we designed the first-in-human dose-finding phase I study of YYB101 in patients with refractory solid tumors. The aim of this study was to determine the maximum tolerate dose (MTD), safety, pharmacokinetics, and pharmacodynamics of YYB101.

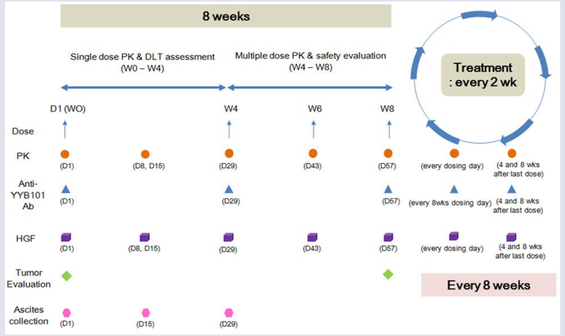
Patients and Method

• Patients
- Patients enrolled in this study had measurable, histologically confirmed metastatic solid cancer.

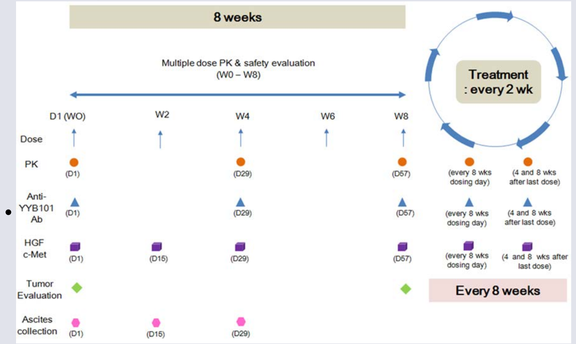
• Method
- YYB101 was administered intravenously at once every 4 weeks until 1 months followed by at once every 2 weeks, for doses of 0.3, 1, 3, 5, 10, 20, 30 mg/kg, according to a 3+3 dose escalation design. Enrolled patients were planned to receive YYB101 until disease progression or intolerable toxicity. The expansion cohort (20mg/kg) was completed (N=17). Pre-planned biomarker analysis was performed in parallel.

Study Scheme

• Dose-escalation cohort



• Dose-expansion cohort



• Dose

Cohort	Level	Dose
Dose escalation	1	0.3 mg/kg
	2	1 mg/kg
	3	3 mg/kg
	4	5 mg/kg
	5	10 mg/kg
	6	20 mg/kg
	7	30 mg/kg
Dose expansion		20 mg/kg (RP2D)

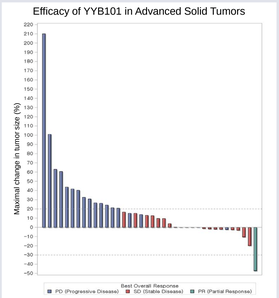
Patients Characteristics (N=39; 12+17)

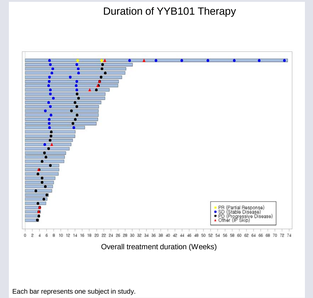
Variables		N (%)
Age	Median	57.0
	Range	23.0-74.0
Gender	Male	16 (41.03)
	Female	23 (58.97)
Tumor types	Gastric cancer	3 (7.69)
	Colon cancer	7 (17.95)
	Rectal cancer	6 (15.38)
	Hepatocellular cancer	1 (2.56)
	Ovarian cancer	10 (25.64)
	Cervical cancer	1 (2.56)
	Lung cancer	1 (2.56)
	Melanoma	4 (10.26)
	Sebaceous carcinoma	2 (5.13)
	Sarcoma	4 (10.26)
Prior lines of chemotherapy	1 regimen	1 (2.56)
	2 regimens	7 (17.95)
	3 regimens	6 (15.38)
	4 regimens	9 (23.08)
	5-9 regimens	16(41.03)
Common metastatic site	Liver	18 (46.15)
	Lung	14 (35.90)
	Lymph nodes	20 (51.28)

Toxicity Profiles (N=39)

Cohort	Toxicity	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
Cohort 1 (N=4, 0.3 mg/kg)	Oral mucositis	0	1	0	0	0
	Fatigue	0	1	0	0	0
	Decreased appetite	0	1	0	0	0
	Azotemia	0	1	1	0	0
	Pruritis	1	0	0	0	0
Cohort 2 (N=3, 1 mg/kg)	Nausea	1	0	0	0	0
	Decreased appetite	1	0	0	0	0
	Pruritis	1	0	0	0	0
Cohort 3 (N=3, 3 mg/kg)	Dizziness	1	0	0	0	0
Cohort 4 (N=3, 5 mg/kg)	Anemia	0	0	1	0	0
	Nausea	1	0	0	0	0
	Decreased appetite	1	0	0	0	0
Cohort 5 (N=3, 10 mg/kg)	Nausea	1	0	0	0	0
	Pruritis	1	0	0	0	0
	Rash	1	0	0	0	0
Cohort 6 (N=3, 20 mg/kg)	Fatigue	1	0	0	0	0
	Decreased appetite	1	0	0	0	0
	Rash	1	0	0	0	0
	Generalized edema	1	0	0	0	0
Cohort 7 (N=3, 30 mg/kg)	Nausea	0	1	0	0	0
	Anemia	0	0	1	0	0
	Generalized edema	0	1	0	0	0
	Thrombocytopenia	0	0	1	0	0
Expansion Cohort (N=17, 20 mg/kg)	Nausea	1	0	0	0	0
	Fatigue	1	1	0	0	0
	Pruritis	2	0	0	0	0
	Rash	0	1	0	0	0
	Anemia	0	1	1	0	0
	Generalized edema	1	3	1	0	0

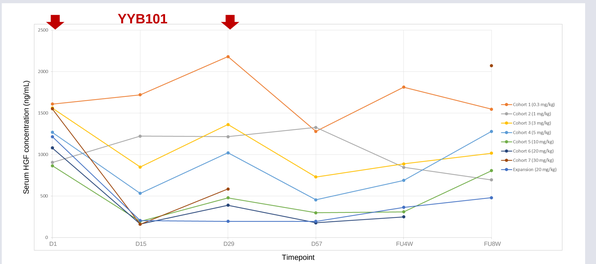
Efficacy Data





• **Of 39 evaluation patients, there was 1 confirmed partial** response **for > +16 months (2.5%, N=1; 1 (of 2) sebaceous carcinoma) and 17 stable disease as best response (43.5%, N=17; 7 (of 13) CRC, 3 (of 4) melanoma, 1 (of 2) sebaceous carcinoma, 1 (of 3) gastric, 1 (of 1) basal cell carcinoma, 2 (of 10) ovarian cancer, 1 (of 1) hepatoma, 1 (of 1) lung cancer)**

YYB101 and HGF levels at cohorts



Conclusions

YYB101 has a favorable safety profile in patients with refractory solid tumors. Efficacy data are encouraging and phase II combination therapy with YYB101 and irinotecan is planned to be open in refractory metastatic CRC patients as salvage treatment.

• **Disclosure of interest conflict : All presenting authors declare that we have no conflicts of interest, including specific financial interests and relationships and affiliations.**