Abstract #3023
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A Phase I Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MSB0254 in Chinese Solid Tumor Patients

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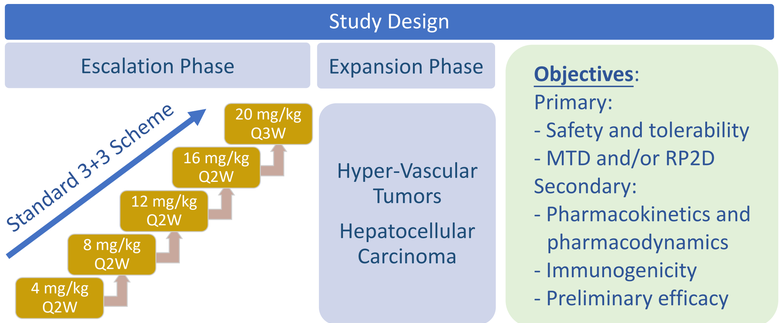
Background:

- Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are key players in tumor angiogenesis signaling pathway. VEGF and VEGFR inhibitors have demonstrated clinical benefit in multiple cancer and eye diseases.
- MSB0254 is a humanized vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody which inhibits angiogenesis induced by either VEGF-A or –C.
- This is a phase I study to evaluate MSB0254's safety, tolerability and PK profiles, as well as preliminary anti-cancer activities in Chinese patients with advanced solid tumors.

Methods:

- This FIH phase I study (NCT04381325) comprises a dose escalation phase and an expansion phase. Patients with locally advanced or metastatic solid tumor and have failed or intolerable to prior standard therapies will be enrolled.



Results:

As of March 10th, 2022, a total of 25 patients were enrolled (table 1) into the dose escalation phase.

Table 1. Patient characteristics

	4 mg/kg Q2W (N=4)	8 mg/kg Q2W (N=3)	12 mg/kg Q2W (N=6)	16 mg/kg Q2W (N=6)	20 mg/kg Q3W (N=6)	Total (N=25)
Age, median (range), years	62 (39, 63)	58 (55, 72)	64 (55, 72)	50.5 (35, 65)	65.5 (54, 73)	60 (39, 73)
Male	2 (50%)	3 (100%)	4 (66.7%)	0	5 (83.3%)	14 (56%)
Primary tumor type						
Gastric Cancer	2 (50%)	0	2 (33.3%)	0	0	4 (16%)
Ovarian Cancer	1 (25%)	0	0	1 (16.7%)	0	2 (8%)
Biliary Tract Cancer	0	0	1 (16.7%)	1 (16.7%)	3 (50%)	5 (20%)
Neuroendocrine Tumor	0	1 (33.3%)	0	0	1 (16.7%)	2 (8%)
Urothelium Carcinoma	0	1 (33.3%)	0	0	0	1 (4%)
Colorectal Cancer	0	1 (33.3%)	0	0	1 (16.7%)	2 (8%)
Non Small Cell Lung Cacner	0	0	1 (16.7%)	0	0	1 (4%)
Cervical Cancer	0	0	1 (16.7%)	0	0	1 (4%)
Epithelioid Hemangioendothelioma	0	0	0	1 (16.7%)	0	1 (4%)
Melanoma	0	0	0	0	1 (16.7%)	1 (4%)
Others	1 (25%)	0	1 (16.7%)	3 (50%)	0	5 (20%)
ECOG						
0	0	1 (33.3%)	1 (16.7%)	3 (50%)	4 (66.7%)	9 (36%)
1	4 (100%)	2 (66.7%)	5 (83.3%)	3 (50%)	2 (33.3%)	16 (64%)
Prior lines of anticancer therapy						
1	0	0	0	1 (16.7%)	2 (33.3%)	3 (12%)
≥2	4 (100.0%)	3 (100.0%)	5 (83.3%)	4 (66.7%)	4 (66.7%)	20 (80%)
Other	0	0	1 (16.7%)	1 (16.7%)	0	2 (8%)

Safety

- One DLT event was observed in the 12 mg/kg Q2W cohort. A subject with intra-cholangial carcinoma developed grade 3 upper gastrointestinal hemorrhage on C1D13. The adverse event was resolved after symptomatic treatment. MTD was not identified.
- A total of 23 (92%) patients experienced treatment emergent adverse events (table 2). One patient with biliary tract carcinoma (20 mg/kg Q3W cohort) experienced upper gastrointestinal hemorrhage and died, which was considered by the investigator to be more likely caused by tumor progression though possibility related to the study drug cannot be ruled out.

Table 2. Summary of TEAEs

	All patients (N=25)
TEAEs	23 (92%)
Serious TEAEs	3 (12%)
Grade ≥3 TEAEs	6 (24%)
TEAEs leading to death	1 (4%)
TEAEs leading to treatment interruption	5 (20%)
TEAEs leading to treatment discontinuation	2 (8%)
DLT	1 (4%)

Figure 1. TEAEs Occurred in ≥5% of Patients

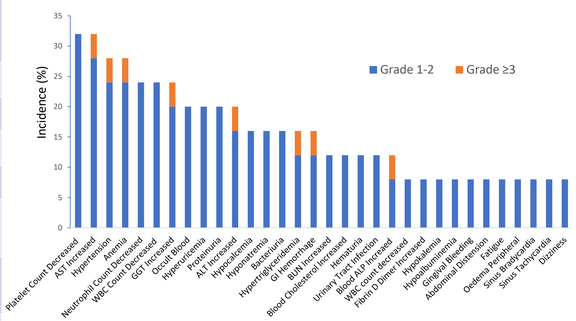
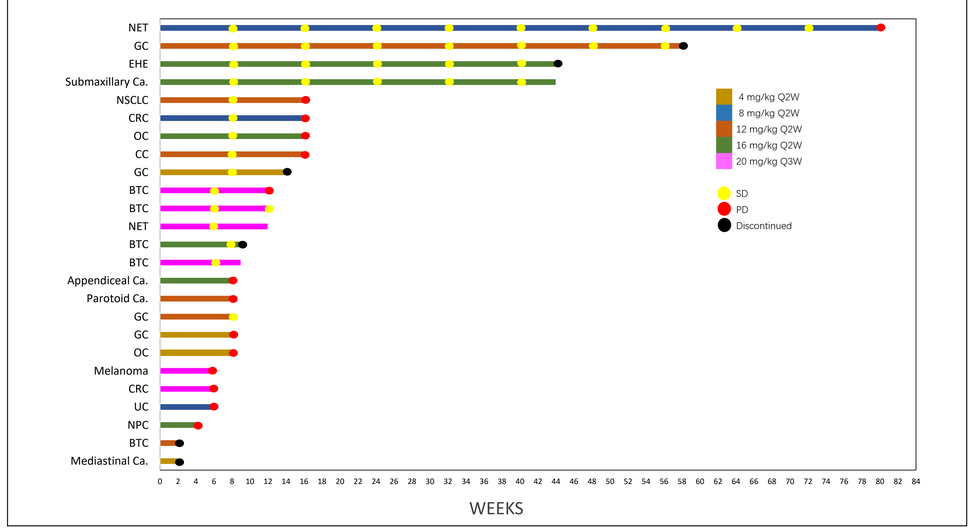


Figure 2. Duration of Treatment



MSB0254 drug exposure and anti-tumor activity

- MSB0254 median treatment duration was 59 (14, 560) days (figure 2).
- Four patients had stable disease more than 6 months (figure2).

Pharmacokinetics and Pharmacodynamics

- Pharmacokinetics analysis showed median Tmax after the first dose was 1.53-3.29h. Serum Cmax and AUC increased proportionately with dose from 4 mg/kg Q2W to 20 mg/kg Q3W (figure 3).
- Population PK simulation supported both 16 mg/kg Q2W and 20 mg/kg Q3W as the recommended phase 2 dose (RP2D) for MSB0254.
- No anti-drug antibody (ADA) were detected in patients across all dose groups.
- Serum concentrations of VEGF-A (figure 4) and sVEGFR-2 (figure5) increased following MSB0254 treatment, without clear relationship with dose.

Figure 3. Mean Serum Concentration - Time Profile (Semi-Log)

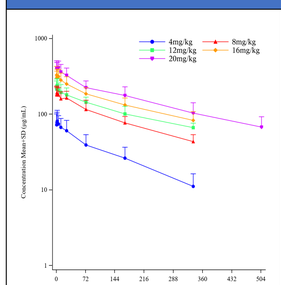


Figure 4. Serum VEGF-A Concentrations Changes (Percentage)

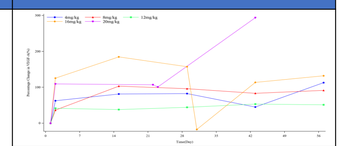
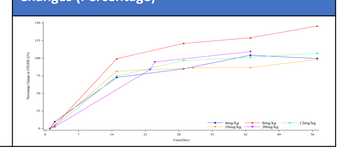


Figure 5. Serum sVEGFR-2 Concentrations Changes (Percentage)



Conclusions and Future Directions of Research:

- MSB0254 demonstrated a manageable safety profile and preliminary antitumor activity in patients with advanced solid tumors. 16mk/kg Q2W and 20 mg/kg Q3W were recommended as RP2D.
- The study of MSB0254 on selected types of tumor warrants further investigation.

Abbreviations:

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate amino transferase; BTC, biliary tract cancer; BUN, blood urea nitrogen; CC, cervical cancer; CRC, colorectal cancer; DLT, dose limiting toxicity; EHE, epithelioid hemangioendothelioma; GC, gastric cancer; GGT, gamma-glutamyl transpeptidase; GI, gastrointestinal; MTD, maximum tolerated dose; NET, neuroendocrine tumor; NPC, nasopharynx cancer; NSCLC, non small cell lung cancer; OC, ovarian cancer; RP2D, recommended phase 2 dose; TEAEs, treatment emergent adverse events; UC, urothelium carcinoma; WBC, white blood cell.