Phase Ib/II, multicenter, single-arm trial of the oral c-Met inhibitor MSC2156119J as monotherapy in patients with Met-positive advanced hepatocellular carcinoma with Child-Pugh class A liver function who failed sorafenib treatment

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ESMO, 26-30 September 2014, Abstract No. 745TiP

Introduction

Background

- HCC is the most common type of liver cancer, which is one of the leading causes of cancer and cancer death worldwide.[1] Incidence is increasing in Western countries.[2]
- Patients with HCC have a poor prognosis.[2] Sorafenib is used first line for advanced HCC, but median survival is 10–11 months and no active therapy is available for use after sorafenib failure.[2]
- The mesenchymal-epithelial transition factor (c-Met) receptor tyrosine kinase is a cell surface receptor mediating cell migration, survival, and proliferation.[3–5]
- c-Met overexpression correlates with aggressive tumor behavior and poor clinical prognosis.[3,4] Inhibition of the Met signaling pathway is therefore a promising therapeutic strategy.
- MSC2156119J is a potent, highly selective c-Met inhibitor. The selectivity of MSC2156119J for c-Met is at least 1,000-fold higher than that for 98% of 242 kinases tested.[6]

Study rationale

- MSC2156119J suppresses growth and induces regression of hepatocyte growth factor (HGF)-dependent and HGF-independent tumors in preclinical models.[6]
- High HGF/c-Met-expressing primary liver explants were sensitive to MSC2156119J monotherapy and antitumor activity was greater than that of sorafenib alone; tumors with low/moderate expression were not sensitive to MSC2156119J.[7]
- An ongoing first-in-man (FIM) trial has demonstrated that MSC2156119J is well tolerated; the maximum tolerated dose was not reached at a dose of 1,400 mg daily.[8]
- Prior studies have demonstrated that HGF/c-Met signaling inhibition has efficacy in patients with Met-overexpressing advanced HCC.[9]

Objectives

Primary objectives

Phase Ib

- To determine the recommended phase II dose (RP2D) of MSC2156119J administered orally once daily over a 21-day cycle in patients with Met+ advanced HCC and Child-Pugh class A liver function in whom sorafenib therapy has failed.

Phase II

- To evaluate progression-free survival (PFS) status at 12 weeks as assessed by the investigator according to RECIST 1.1 in patients with advanced HCC and Child-Pugh class A liver function in whom sorafenib therapy has failed.

Secondary objectives

Phase Ib

- To characterize the single and multiple dose pharmacokinetics (PK), antitumor activity and biochemical response, and safety and tolerability of MSC2156119J.

Phase II

- To evaluate the antitumor activity, biochemical response, and safety and tolerability of MSC2156119J.

Methods

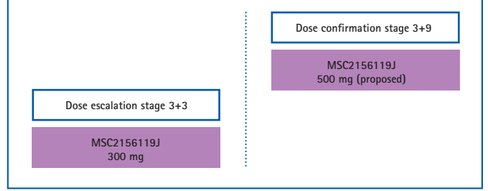
Study design

- This study is registered at clinicatrials.gov (NCT02115373).

Phase Ib

- Open-label, single-arm, dose-escalation trial conducted in at least four centers in Europe.
- Classic 3+3 trial design with a dose-escalation and dose-confirmation stage **(Figure 1)**.
- Up to 18 patients will be enrolled in two dose cohorts.
- Dose escalation will depend on whether dose-limiting toxicities (DLTs) occur. These are predefined as:
  - Grade 4 neutropenia for >7 days
  - Grade ≥3 neutropenia for >1 day
  - Grade 4 thrombocytopenia or grade 3 thrombocytopenia with non-traumatic bleeding
  - Grade ≥3 uncontrolled nausea/vomiting and/or diarrhea despite optimal treatment for >3 days
  - Any grade ≥3 non-hematologic adverse event except the above gastrointestinal events and alopecia
  - Adverse events considered by the investigators to be related to underlying disease, medical conditions, and concomitant therapy are not considered DLTs.

Figure 1. Phase Ib design



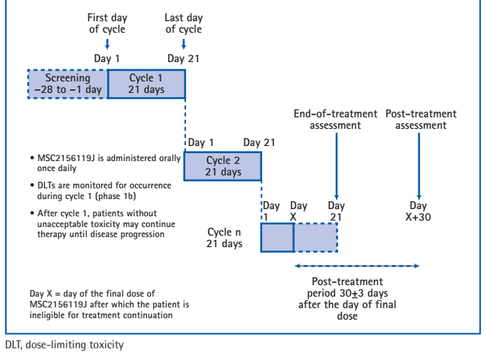
Phase II

- Single-arm, multicenter trial conducted in approximately 15 centers in Europe.
- Patients receive MSC2156119J once daily at the RP2D determined from the phase Ib study until disease progression, intolerable toxicity, death, or withdrawal of consent.
- A total of 48 patients will be enrolled.

Patient screening

- Informed consent will be obtained before any patient assessment.
- Eligibility screening will be performed within 28 days of the first dose of MSC2156119J **(Figure 2)**.
- Assessments will include tumor imaging, assessment of Met status, medical history, and concomitant medication.

Figure 2.



DLT, dose-limiting toxicity

Study treatment

- Patients will receive MSC2156119J once daily at the assigned dose, in the morning after breakfast, for the duration of each 21-day cycle **(Figure 2)**.

Patient eligibility criteria

Key inclusion criteria

- Adults aged ≥18 years with histologically or cytologically confirmed HCC.
- Child-Pugh class A.
- ECOG PS status 0–1.
- Previously treated with sorafenib for ≥4 weeks and discontinued sorafenib treatment due to intolerability or radiographic disease progression ≥14 days prior to day of study treatment.
- Life expectancy of ≥3 months as judged by the investigator.
- Availability of a pretreatment tumor biopsy taken after discontinuation of sorafenib and within 28 days of the first dose of MSC2156119J.
- For the phase II study, Met+ status as defined based on c-Met protein overexpression (moderate [2+] or strong [3+] staining intensity for c-Met in the majority [>50%] of tumor cells by immunohistochemistry).
- Measurable disease in accordance with RECIST v 1.1.
- Written informed consent by all patients prior to any study-specific procedure.

Key exclusion criteria

- Prior systemic anticancer treatment for advanced HCC except for sorafenib.
- Prior treatment with agents targeting the HGF/c-Met pathway.
- Prior loco-regional therapy within 4 weeks prior to Day 1 of trial treatment.
- Peripheral neuropathy grade ≥2.
- Prior history of liver transplant.
- Impaired cardiac function or uncontrolled hypertension.
- Prior or current history of neoplasms other than HCC.
- Clinically significant gastrointestinal bleeding within 4 weeks of trial entry.

End of treatment and follow-up

End of treatment

- MSC2156119J treatment will be discontinued due to disease progression, intolerable toxicity, or withdrawal of consent.
- Evaluations include tumor biopsy, physical examination, ECOG performance status, adverse events, concomitant medication, vital signs, ECG, blood samples for hematology, coagulation, and chemistry, urinalysis, complete tumor assessment of all lesions (if previous assessment was ≥6 weeks previously), serum AFP, and blood samples for exploratory markers.
- For phase II, FHSI-8 and patient-reported outcomes (FACT-HP) will also be assessed.

Post-treatment follow-up

- The post-treatment follow-up visit will be performed 30 ±3 days after the last dose for those who discontinue study medication permanently.
- Assessments include: physical examination, ECOG performance status, adverse events, ECG, blood samples for hematology, coagulation, and chemistry, and urinalysis.
- For phase II, FHSI-8 and patient-reported outcomes (FACT-HP) will also be assessed.
- Survival data will be collected every 3 months ±2 weeks after the end of treatment until death, withdrawal of consent, or study end.

Statistical considerations

- For phase II, the null hypothesis is that the PFS rate at 12 weeks will be ≤15% and will be tested against the one-sided alternative keeping a one-sided error of 5%.
- The null hypothesis will be rejected and the trial will meet its primary endpoint if ≥12 patients are progression free at 12 weeks.

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Acknowledgments

The trial was sponsored by Merck KGaA, Darmstadt, Germany. The authors would like to thank patients, investigators, co-investigators and the study teams at each of the participating centers and at Merck KGaA, Darmstadt, Germany and Merck Serono SA - Geneva, Switzerland*. Medical writing assistance was provided by Andy Noble, Bioscript Science, Macclesfield, UK and funded by Merck KGaA, Darmstadt, Germany.

Disclosures

SR is a consultant for Merck. **BS** and **AJ** are employees of Merck KGaA, Darmstadt, Germany. **HZ** is an employee of EMD Serono, Boston, MA, USA. **ER** has declared no conflict of interest.

*An affiliate of Merck KGaA, Darmstadt, Germany.

MSC2156119J is currently under clinical investigation and has not been approved by any regulatory authority. Status: September 2014.