Phase Ib/II trial of c-Met inhibitor MSC2156119J and gefitinib vs chemotherapy as 2nd-line treatment in Asian patients with Met-positive (Met+), locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor mutation (EGFRm+) and progression on gefitinib

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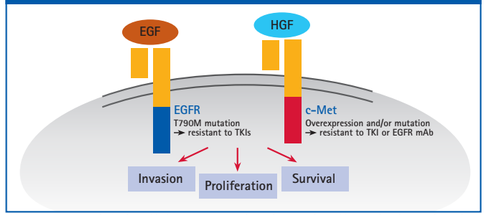
Introduction

Background

- Lung cancer is one of the leading causes of cancer death worldwide. Approximately 85% of all lung cancer patients have NSCLC.
- Novel targeted therapies have been developed for the treatment of selected NSCLC patients with EGFR mutation, including the oral EGFR tyrosine kinase inhibitor (EGFR TKI) gefitinib.
- EGFR TKIs block the signal transduction pathways involved in the proliferation and survival of cancer cells.[1]
- The main reason for developing resistance to EGFR TKIs is a secondary mutation in the EGFR gene (T790M mutation, 50%) and amplification of the c-Met proto-oncogene (20%) (**Figure 1**).[2,3]
- c-Met overexpression and c-Met gene mutation are likely to occur in NSCLC patients and are associated with poor prognosis.[4]
- MSC2156119J is a potent, highly selective c-Met inhibitor that reduces tumor growth. In addition, it induces regression of hepatocyte growth factor (HGF)-dependent and HGF-independent tumors in preclinical models.[5] MSC2156119J is currently under investigation in an ongoing first-in-man (FIM) trial,[6] which identified an MSC2156119J dose of 500 mg/day for further study and for which an expansion cohort at this dose is being enrolled.

Figure 1. Resistance to EGFR TKIs in NSCLC patients



EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.

Study rationale

- The FIM study confirmed the safety and tolerability of MSC2156119J monotherapy, and nonclinical studies demonstrated mechanisms of dual inhibition of c-Met and EGFR pathways after acquired resistance to first-line EGFR TKI treatment.
- The phase Ib dose-escalation part of the study, prior to the phase II, is considered a safety run-in to determine the recommended phase II dose (RP2D) of MSC2156119J in combination with EGFR TKI (gefitinib).
- In the randomized phase II part of the present study, the antitumor activity of MSC2156119J is evaluated in combination with an EGFR TKI (gefitinib) and compared with the current optimal chemotherapy for non-squamous NSCLC (pemetrexed + cisplatin).

Objectives

Primary objectives

Phase Ib

- Determine the RP2D of MSC2156119J when used in combination with gefitinib (at the approved standard dose of 250 mg) when administered orally once daily over a 21-day cycle in patients with Met+ advanced NSCLC.

Phase II

- Evaluate whether the efficacy in terms of progression-free survival (PFS) in the T790M-positive/intermediate or -negative stratum treated with second-line MSC2156119J in combination with gefitinib is superior to that of pemetrexed + cisplatin in patients with EGFR-mutated, Met+ advanced NSCLC with acquired resistance to first-line gefitinib. The two strata (T790M positive/intermediate and T790M negative) will be analyzed separately.

Secondary objectives

Phase Ib

- Characterize the pharmacokinetics (PK) of MSC2156119J when given in combination with gefitinib.
- Characterize the PK of gefitinib when given in combination with MSC2156119J.
- Assess the safety and tolerability of MSC2156119J in combination with gefitinib.
- Evaluate preliminary antitumor activity of MSC2156119J in combination with gefitinib.

Phase II

- Evaluate the safety and tolerability of MSC2156119J in combination with gefitinib.
- Evaluate the efficacy of MSC2156119J in combination with gefitinib in the two strata defined by T790M status (T790M positive/intermediate and T790M negative).

Methods

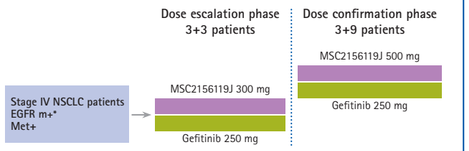
Study design

- The study is registered at clinicaltrials.gov (NCT01982955).

Phase Ib

- Open-label, single-arm, dose-escalation study in multiple centers in China, South Korea, Taiwan, and other Asian countries.
- Classic 3+3 design, with a dose-escalation phase and a dose-confirmation phase (**Figure 2**).
- Dose escalation and de-escalation are based on the occurrence of dose-limiting toxicities (DLTs) in cycle 1.
- A total of 15–18 patients are planned to be enrolled.
- Anticipated dose cohorts of MSC2156119J are 300 mg and 500 mg once daily; gefitinib will be co-administered at 250 mg once daily.
- PK sampling will be performed to characterize the PK profile of MSC2156119J and gefitinib.

Figure 2. Phase Ib design

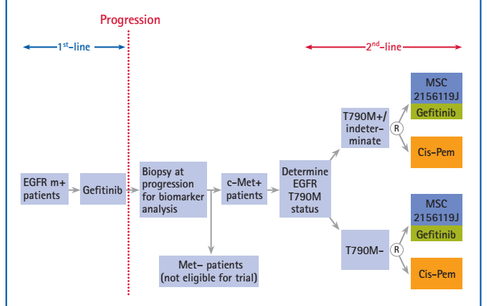


* Only required for patients who are eligible for first-line gefitinib treatment.

Phase II

- This randomized, multicenter, open-label, active-controlled phase will be conducted once the RP2D has been determined in phase Ib.
- Patients are enrolled into two predefined subgroups depending on T790M status.
- A total of 200 patients will be enrolled to either a T790M-positive/intermediate subgroup (100 patients) or a T790M-negative subgroup (100 patients).
- Within each subgroup, patients are randomized 1:1 to 250 mg gefitinib + RP2D MSC2156119J (experimental arm) or 75 mg/m^2 cisplatin + 500 mg/m^2 pemetrexed (control arm; **Figure 3**).
- An interim analysis is planned when 50% of target events that allow for the analysis of PFS have occurred in each T790M subgroup.
- PK sampling is performed to identify covariates that might explain variability in the pharmacokinetics of MSC2156119J.

Figure 3. Phase II randomization scheme

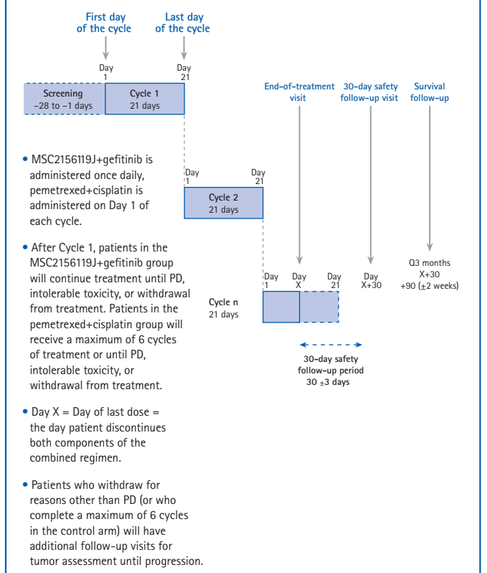


Cis, cisplatin; EGFRm+, epidermal growth factor mutation positive; Pem, pemetrexed.

Treatment duration

- Screening of patients will take place up to 28 days prior to study treatment.
- Patients receive MSC2156119J + gefitinib until progression of disease (PD), intolerable toxicity, or withdrawal of consent.
- In the control arm of phase II, pemetrexed + cisplatin are administered on day 1 of each cycle for a maximum of 6 cycles. **Figure 4** shows the treatment duration in phase II.
- An end-of-treatment visit will take place within 14 days of the last dose.
- A safety follow-up visit will occur at 30 ±3 days after the last dose.
- In phase II, additional survival follow-up assessments will be performed every 3 months ± 2 weeks until death or end of the trial.

Figure 4. Treatment duration in phase II



- MSC2156119J+gefitinib is administered once daily, pemetrexed+cisplatin is administered on Day 1 of each cycle.
- After Cycle 1, patients in the MSC2156119J+gefitinib group will continue treatment until PD, intolerable toxicity, or withdrawal from treatment. Patients in the pemetrexed+cisplatin group will receive a maximum of 6 cycles of treatment or until PD, intolerable toxicity, or withdrawal from treatment.
- Day X = Day of last dose = the day patient discontinues both components of the combined regimen.
- Patients who withdraw for reasons other than PD (or who complete a maximum of 6 cycles in the control arm) will have additional follow-up visits for tumor assessment until progression.

PD, progression of disease.

Patient eligibility criteria

Key inclusion criteria

- Adults with histologically or cytologically confirmed advanced NSCLC, regardless of histology subtype.
- Pretreatment tumor biopsy.
- Confirmed Met+ status, defined as c-Met protein overexpression, ie, moderate (2+) or strong (3+) staining intensity for c-Met in the majority (≥50%) of tumor cells using immunohistochemistry.
- ECOG PS status 0–1.
- Activating mutation of EGFR and results of EGFR T790M mutation testing available (positive/intermediate/negative; phase II only).
- Resistance to first-line gefitinib (phase II only).
- Written informed consent by all patients prior to any study-specific procedure.

Key exclusion criteria

- Life expectancy of <3 months.
- Inadequate bone marrow, liver, or renal function.
- Prior systemic chemotherapy or agents targeting EGFR pathway other than gefitinib (phase II only).

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Acknowledgments

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Disclosures

YW and KP have nothing to disclose. JY has a consultancy/advisory role for Merck. LX was an employee of Merck Serono, Beijing, China when this trial was designed. US and AJ are employees of Merck KGaA, Darmstadt.

* 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.