



HUTCHISON CHINA MEDITECH LIMITED

Press Release

Sulfatinib clinical results and fruquintinib-savolitinib combination preclinical results to be presented at the 2015 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics conference

London: Friday, 30 October 2015: Hutchison China MediTech Limited (“Chi-Med”) (AIM: HCM) today announces that Hutchison MediPharma Limited (“HMP”), its drug R&D subsidiary, will present further scientific data on sulfatinib (HMPL-012), fruquintinib (HMPL-013) and savolitinib (AZD6094, HMPL-504) at the International Conference on Molecular Targets and Cancer Therapeutics, which will be held in Boston, Massachusetts, USA from 5 to 9 November 2015. Sulfatinib, fruquintinib and savolitinib were all discovered by HMP and are currently being evaluated in clinical trials for the treatment of various cancers.

Sulfatinib is an oral drug candidate that selectively inhibits the tyrosine kinase activity associated with the vascular endothelial growth factor receptor (“VEGFR”) and fibroblast growth receptor (“FGFR”), a receptor for a protein which also plays a role in tumour growth. HMP will present clinical data from its Phase I trial in China, focusing on neuroendocrine tumour (“NET”) patients. In this study, sulfatinib’s objective response rate among the 18 efficacy-evaluable NET patients was 44.4% and disease control rate was 100%. By comparison, sunitinib and everolimus, the two approved single agent therapies for neuroendocrine tumours, achieve objective response rates of less than 10% in their pivotal clinical trials. Furthermore, neuroendocrine tumour responses to sulfatinib have been observed to improve gradually with time.

Savolitinib is an inhibitor of the c-Met receptor tyrosine kinase, an enzyme which has been shown to function abnormally in many types of solid tumours, and fruquintinib is a highly selective inhibitor of VEGFR1, 2 and 3. In clear cell renal cell carcinoma (“ccRCC”), c-Met activation has emerged as one of the mechanisms for resistance to anti-VEGF/VEGFR therapies, implying that inhibition of the c-Met and VEGFR pathways in a combination therapy could produce additional clinical benefit. HMP will present data from a preclinical study to assess the effect of savolitinib and fruquintinib combined in ccRCC xenograft models. In this study, while single-agent treatment at clinically relevant doses only exhibited mild to moderate tumour growth inhibition, a significantly increased anti-tumour effect was observed for the group receiving combination therapy.

Preclinical data will also be presented regarding savolitinib in non-small cell lung cancer (“NSCLC”) and mechanisms of acquired savolitinib resistance.

The following posters will be made available at www.chi-med.com/news/ after they are presented at the conference:

- 1st Presentation*
Title: **First-in-human phase I study of a selective VEGFR/FGFR dual inhibitor sulfatinib in patients with advanced solid tumours**
- Authors:* Jian-Ming Xu, et al.
- Session:* Poster Session A – Angiogenesis and Antiangiogenesis Agents
- Date & Time:* Friday 6 November 2015, 12:15 PM – 3:15 PM
- 2nd Presentation*
Title: **Synergistic effect of c-Met inhibitor Savolitinib in combination with a VEGFR inhibitor Fruquintinib in clear cell renal cell carcinoma xenograft models**
- Authors:* Yongxin Ren, et al.
- Session:* Poster Session B –Therapeutic Agents: Small Molecule Kinase Inhibitors
- Date & Time:* Saturday 7 November 2015, 12:30 PM – 3:30 PM
- 3rd Presentation*
Title: **Acquired resistance to the cMET inhibitor savolitinib in lung cancer models through EGFR/mTOR/MYC deregulation and adoption of PIM signalling**
- Authors:* Ryan Henry, et al.
- Session:* Late-Breaking Poster Session – Drug Resistance and Modifiers
- Date & Time:* Sunday 8 November 2015, 12:30 PM – 3:30 PM

Hosted by the American Association for Cancer Research (“AACR”), the National Cancer Institute (“NCI”), and the European Organisation for Research and Treatment of Cancer (“EORTC”), the 2015 Molecular Targets and Cancer Therapeutics conference will bring together an estimated 3,000 academics, scientists, and pharmaceutical industry representatives from across the globe to discuss innovations in drug development, target selection, and the impact of new discoveries in molecular biology.

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Enquiries

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Notes to Editors

Abstracts

Title: *First-in-human phase I study of a selective VEGFR/FGFR dual inhibitor sulfatinib in patients with advanced solid tumours*

Authors: Jian-Ming Xu, Lin Shen, Yan Wang, Yu-ling Chen, Ru Jia, Jian Wang, Ke Li, Yang Sai, Jing Li, Chuan Qi, Hua Ye, Su Weiguo

Background: Sulfatinib is a highly selective oral small molecule inhibitor targeting both vascular endothelial growth factor receptors (VEGFR) and fibroblast growth factor receptors (FGFR). A phase I dose-escalation study was carried out to determine sulfatinib maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), pharmacokinetic (PK) profiles, and preliminary antitumor activity in patients with advanced solid tumours.

Methods: Sulfatinib was administered orally in 28-day treatment cycles until disease progression or unacceptable toxicity. The study utilized 3+3 dose escalation method, with ascending dose cohorts from 50mg to 350mg daily. During the study, a milled formulation was developed to reduce the inter-patient PK variations and optimize drug absorption. The milled formulation was used in 200mg once daily (QD) to 350mg QD dose cohorts.

Results: As of July 6, 2015, a total of 77 patients had been enrolled. Forty-three of the 77 patients received original formulation in dose cohorts from 50mg to 300mg daily. The data of patients treated with original formulation dosing from 50 to 300mg once daily, or 125mg and 150mg twice daily were reported in ASCO 2012(#3040). Thirty-four of the 77 patients received milled formulation. Among the 34 patients, 23 were enrolled in the dose-escalation phase, receiving sulfatinib 200mg to 350mg QD whereas 11 patients were enrolled in the dose-expansion phase receiving sulfatinib 300mg or 350 mg QD. Among the 34 patients, there were 24 male patients (70.6%) and 10 female patients (29.4%). The median age was 55.97 (23.35-73.17) years. The most common adverse events of 34 patients were hypertension, proteinuria, diarrhoea, elevated AST/ALT and decreased blood albumin, mostly grade 1/2. One DLT (grade 3 ALT/AST increase) was observed in the 200 mg QD dose group. MTD was not reached up to 350mg QD. Among the 34 subjects treated with milled formulation, 22 subjects were diagnosed with neuroendocrine tumours (NETs). Eight NET patients (5 in 300mg QD and 3 in 350mg QD cohort) had confirmed partial response (PR) with median duration of response (DoR) of 13.8 months. The tumour origins of the 8 NET patients include pancreas (3 patients), duodenum (1 patient), rectum (1 patient), thymus (1 patient) and unknown origin (2 patients). Objective response rate among the 18 efficacy evaluable NET patients was 44.4% and disease control rate was 100%. Sulfatinib half-life ($t_{1/2}$) in plasma averaged 14-20 hours at the test dose levels, which supported sulfatinib QD dosing frequency. Following QD multiple dosing, sulfatinib achieved steady state on Day 14. The drug exposure increased when the dose increased from 200 mg to 300 mg, and then plateaued from 300 mg to 350 mg. Based on the clinical safety, efficacy, and PK data, the recommended Phase II dose is determined to be 300 mg QD.

Conclusions: Sulfatinib was well tolerated with an acceptable safety profile. Promising anti-tumour activity was observed in NET patients. Further clinical studies with sulfatinib are warranted.

Title: *Synergistic effect of c-Met inhibitor Savolitinib in combination with a VEGFR inhibitor Fruquintinib in clear cell renal cell carcinoma xenograft models*

Authors: Yongxin Ren, Shiming Fan, Yunxin Chen, Renxiang Tang, Wei Zhang, Jianxing Tang, Linfang Wang, Dongxia Shi, Hongbo Chen, Min Cheng, Weiguo Qing, Weiguo Su

Renal cell carcinoma (RCC) is the most common type of kidney tumour in human. Approximately 80~85% of RCC is clear cell renal cell carcinoma (ccRCC). Although VEGF/VEGFR targeted therapies bring significant advances in the treatment of RCC, ultimate resistance occurs in most cases following a transient period of clinical benefit. The hepatocyte growth factor (HGF) receptor c-Met activation emerges as one of the mechanisms for resistance to anti-VEGF/VEGFR therapies in ccRCC, implying that a combinational inhibition of c-Met and VEGFR pathways may induce a synergistic anti-tumour effect and could produce additional clinical benefit. The aim of this study was to assess the effect of a combination strategy targeting the VEGFR and c-MET pathways in ccRCC xenograft models.

Savolitinib (AZD6094, HMPL-504) is a highly selective inhibitor against c-Met. Fruquintinib (HMPL-013) strongly inhibits VEGFR1, 2 and 3. Both of them were discovered by HMP and are currently being evaluated in clinical trials for the treatment of various cancers. Several subcutaneous xenograft models were established in nude mice with human ccRCC cell lines or patient derived tumours (PDX) to investigate the anti-tumour effect of combination of savolitinib with fruquintinib. Treatment with savolitinib or fruquintinib at clinically relevant dose only exhibited mild to moderate tumour growth inhibition as a single agent in all of tested models, but significantly increased anti-tumour effect was observed in all of tested models for the combination group. It seemed that the enhanced anti-tumour effect was associated with c-Met inhibition. In a ccRCC PDX model KIN1T1342, the increased anti-tumour effect was correlated with dose increment of savolitinib. Immunohistochemistry (IHC) analysis revealed that combination treatment produced stronger inhibition on tumour proliferation marker Ki67 and angiogenesis marker CD31, compared to either savolitinib or fruquintinib alone, indicating that the observed synergistic effect might be attributed to the dual inhibition on tumour signalling and tumour microenvironment. C-Met expression was observed in all tested models, and treatment with savolitinib effectively suppressed phospho-MET.

To evaluate c-Met expression in Chinese ccRCC patients, Formalin-Fixed and Paraffin-Embedded (FFPE) tumour sections were collected from sixty-two treatment-naive patients during surgical resection. Positive c-Met expression was found in 69% (43/62) of ccRCC samples under IHC staining.

Overall our data demonstrated that c-Met was widely expressed in Chinese ccRCC patients and provided a rationale to test the combined HGF/c-Met and VEGF/VEGFR pathway blockade in the treatment of ccRCC in the clinical trials.

Title: Acquired resistance to the cMET inhibitor savolitinib in lung cancer models through EGFR/mTOR/MYC deregulation and adoption of PIM signalling

Authors: Ryan E. Henry, Evan R. Barry, Brendon Ladd, Aleksandra Markovets, Garry J. Beran, Yongxin Ren, Feng Zhou, Lillian Castriotta, Ammar Adam, Weiguo Qing, Weiguo Su, Edwin Clark, Celina M. D'Cruz, Alwin Schuller.

Lung cancer is the most common cause of cancer death globally with a significant, unmet need for more efficacious treatments. Aberrant receptor tyrosine kinase (RTK) signalling is a well-documented driver of disease onset and progression in multiple cancer types, including NSCLC, where the cMET RTK contributes to tumour progression, maintenance and resistance to targeted therapies. Here, we explore the therapeutic potential of the potent and selective cMET inhibitor savolitinib (volitinib, AZD6094, HMPL-504) in NSCLC and begin to elucidate mechanisms of acquired savolitinib resistance in preclinical models. Using in vitro proliferation assays and immunoblot analysis, we determine that savolitinib rapidly inhibits cMET auto-phosphorylation/activation and reduces the viability of NSCLC cell lines NCI-H1993 and EBC-1 with a GI_{50} of 4.20 nM and 2.14 nM, respectively. In vivo, once daily treatment of NCI-H1993 xenografts with 3.0 mg/kg savolitinib significantly slows tumour growth, whereas treatment of EBC-1 xenografts with 30.0 mg/kg results in tumour stasis. Importantly, we observe tumour regressions in a patient-derived xenograft model of a NSCLC lymph node metastasis, HLXF-036LN, dosed with savolitinib 50.0 mg/kg once daily. Pharmacodynamic analysis of in vitro and in vivo models shows that savolitinib sensitivity correlates with blockade of PI3K/AKT and MAPK signalling, and interestingly, with cMYC (MYC) protein down-regulation. To elucidate mechanisms of acquired resistance in NSCLC, we generated savolitinib resistance in vitro using the NCI-H1993 and EBC-1 cell lines and further sub-cloned resistant NCI-H1993 cells to study the heterogeneity of resistance mechanisms. Using small-molecule screening, phospho-protein arrays and interrogation of signalling pathway activity by immunoblot, we identify 1) deregulated mTORC1/2 signalling and 2) the uncoupling of MYC expression from cMET activation as commonly contributing to resistance in all clones tested. RNA interference (siRNA) and MYC over-expression experiments confirm the novel finding that sustained MYC expression can partially drive resistance to a tyrosine kinase inhibitor such as savolitinib. Additionally, we identify clone-specific resistance mechanisms arising via a previously-described switch to EGFR dependence or by our novel finding of a de novo requirement for PIM signalling. Taken together, this work demonstrates the preclinical efficacy of savolitinib in NSCLC and provides an initial characterization of potential resistance mechanisms, identifying core resistance targets and clone-specific vulnerabilities that could be exploited to counter acquired savolitinib resistance that may emerge in the clinic.

About sulfatinib

Sulfatinib is an oral drug candidate that selectively inhibits the tyrosine kinase activity associated with VEGFR and FGFR. Angiogenesis is an important mechanism in tumour pathogenesis, and inhibition of VEGF-mediated angiogenesis has been important in the treatment of a variety of cancers. FGFR is a receptor for a protein which also plays a role in tumour growth. HMP is conducting, or in the process of initiating, two Phase III and two Phase Ib clinical trials in China, and one Phase I clinical trial in the United States. These trials are intended to assess the effectiveness of sulfatinib for the treatment of neuroendocrine cancer and thyroid cancer patients.

About fruquintinib

Fruquintinib is designed as a highly selective and potent oral inhibitor of VEGFR, namely VEGFR1, VEGFR2, and VEGFR3. In March and September 2015, Chi-Med announced that the first proof-of-concept studies of fruquintinib in China in patients with third-line metastatic colorectal cancer and non-small cell lung cancer clearly met their primary endpoints of progression free survival by demonstrating superiority compared with placebo. Fruquintinib was well tolerated in both studies, showing no major unexpected safety issues. HMP is conducting or in the process of initiating two Phase III clinical trials in these indications. HMP is also conducting a Phase Ib dose-finding study of fruquintinib, in combination with paclitaxel, in second line gastric cancer patients in China.

In October 2013, HMP entered into a licensing, co-development and commercialisation agreement with Eli Lilly for fruquintinib.

About savolitinib

Savolitinib is a potential global first-in-class inhibitor of c-Met, receptor tyrosine kinase, an enzyme which exhibits aberrant behaviour (e.g. gene amplification, over-expression and mutation) in many types of solid tumours. Savolitinib was developed as a potent and highly selective oral c-Met inhibitor that was designed to address renal toxicity, the primary issue that has to-date prevented other selective c-Met inhibitors from gaining regulatory approval. In Phase I/Ib clinical studies in Australia and China, savolitinib has shown promising signs of clinical efficacy, causing tumour size reduction, in c-Met aberrant patients in papillary renal cell carcinoma, non-small cell lung cancer, colorectal cancer and gastric cancer.

Currently, HMP and AstraZeneca AB, its partner on savolitinib, are conducting nine clinical studies of savolitinib monotherapy treatment as well as savolitinib in combination treatments with other tyrosine kinase inhibitors and chemotherapy in kidney, lung and gastric cancers. Furthermore, by the end of 2015, HMP and AstraZeneca AB expect to initiate three further proof-of-concept studies for savolitinib, two of which will involve combinations with immunotherapies.

About Chi-Med

Chi-Med is a China-based, globally-focused healthcare group which researches, develops, manufactures and sells pharmaceuticals and health-related consumer products. Its Innovation Platform focuses on discovering and developing innovative therapeutics in oncology and autoimmune diseases for the global market. Its Commercial Platform manufactures, markets and distributes prescription drugs and consumer health products in China.

Chi-Med is majority owned by the multinational conglomerate CK Hutchison Holdings Limited (SEHK: 0001). For more information, please visit: www.chi-med.com.

Forward-Looking Statements

This announcement contains forward-looking statements that reflect Chi-Med's current expectations regarding future events, including its plans to initiate clinical studies for its drug candidates in the targeted indications, its expectations as to whether such studies would meet their primary or secondary endpoints, and its expectations as to the timing of the completion and the release of results from such studies. Forward-looking statements involve risks and uncertainties. Such risks and uncertainties include, among other things, assumptions regarding enrolment rates, timing and availability of subjects meeting a study's inclusion and exclusion criteria, changes to clinical protocols or regulatory requirements, unexpected adverse events or safety issues, the ability of a drug candidate to meet the primary or secondary endpoint of a study, the ability of a drug candidate to obtain regulatory approval in different jurisdictions, the ability of a drug candidate to gain commercial acceptance after obtaining regulatory approval and the sufficiency of funding. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Chi-Med undertakes no obligation to update or revise the information contained in this announcement, whether as a result of new information, future events or circumstances or otherwise.