



HUTCHISON CHINA MEDITECH LIMITED

Press Release

Chi-Med Presented Pre-clinical Data for Fruquintinib and Sulfatinib at the American Association for Cancer Research Annual Meeting 2017

London: Friday, April 7, 2017: Hutchison China MediTech Limited (“Chi-Med”) (AIM/Nasdaq: HCM) presented pre-clinical data for fruquintinib and sulfatinib at the American Association for Cancer Research (“AACR”) Annual Meeting 2017, held in Washington, D.C., USA from April 1 to 5, 2017. Fruquintinib and sulfatinib are both being evaluated in Phase III clinical trials for various cancers.

Fruquintinib is designed to be a highly selective and potent oral inhibitor of vascular endothelial growth factor receptors (“VEGFR”) with a tolerability profile that enables rational combination with other cancer therapies. A new drug application (“NDA”) for fruquintinib to the China Food and Drug Administration (“CFDA”) is expected to be filed in mid-2017. It is currently under the joint development in China by Chi-Med and its partner Eli Lilly and Company (“Lilly”).

Sulfatinib is an oral, novel angio-immunokinase inhibitor that selectively targets VEGFR, fibroblast growth factor receptor (“FGFR”) and colony-stimulating factor-1 receptor (“CSF-1R”), three key tyrosine kinase receptors involved in tumor angiogenesis and immune evasion. Two Phase III trials are underway in neuroendocrine tumor (“NET”) patients in China.

The presentations were as follows:

- Presentation Title:** Evaluation of fruquintinib, a potent and selective oral VEGFR inhibitor, in combination with targeted therapies or immune checkpoint inhibitors in preclinical tumor models
- Authors:** Yongxin Ren et al.
- Abstract:** #2089
- Session:** Growth Factor and Hormone Receptors as Therapeutic Targets
- Date & Time:** Monday, April 3, 2017, 1:00 PM (EST)
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- Presentation Title:** Preclinical evaluation of sulfatinib, a novel angio-immuno kinase inhibitor targeting VEGFR, FGFR1 and CSF-1R kinases
- Authors:** Jinghong Zhou et al.
- Abstract:** #4187
- Session:** Targeting Protein Kinases and DNA Repair
- Date & Time:** Tuesday, April 4, 2017, 1:00 PM (EST)

The presentations are available at www.chi-med.com/news/. Further information about AACR is available at aacr.org.

ABSTRACTS

Evaluation of fruquintinib, a potent and selective oral VEGFR inhibitor, in combination with targeted therapies or immune checkpoint inhibitors in preclinical tumor models

Authors: Yongxin Ren, Qiaoling Sun, Jingwen Long, Shiming Fan, Renxiang Tang, Wei Zhang, Xuelei Ge, Jianxing Tang, Linfang Wang, Dongxia Shi, Hongbo Chen, Min Cheng, Weiguo Qing and Weiguo Su

The development of therapies targeting tumor angiogenesis, tumor driver gene alterations and tumor immune evasion has made tremendous advancement in improving overall survival ("OS"). However, efficacy may be limited and resistance often develops rapidly when targeting a single axis of tumorigenesis. Therefore, it is worthwhile to explore rational combination of therapies based on tumor-specific features. Fruquintinib is a potent and selective oral VEGFR inhibitor currently in Phase III clinical trials for non-small-cell lung cancer ("NSCLC") and colorectal cancer ("CRC"). We report here the evaluation of anti-tumor effect of fruquintinib in preclinical animal tumor models in combination with therapies targeting tumor driver gene alterations such as epidermal growth factor receptor ("EGFR") and mesenchymal growth factor receptor ("c-MET") or with immune checkpoints.

In NSCLC xenograft models with EGFR activation such as activating mutations, gene amplification or protein overexpression, fruquintinib plus an EGFR tyrosine kinase inhibitor such as gefitinib or thelialtinib (HMPL-309) was found to be more efficacious than either monotherapy. For instance, in PC-9 subcutaneous tumor model carrying EGFR exon 19 deletion, single agent treatment with fruquintinib at 2 mg/kg and gefitinib at 5 mg/kg produced the tumor growth inhibition ("TGI") of 58% and 63%, respectively, while the combination treatment resulted in a TGI of 100% and tumor regression was observed in 11 of 16 mice treated with combinational therapy. In multiple xenograft models derived from lung cancer or renal cell cancer with c-MET activation (amplification or over-expression), addition of fruquintinib to a c-MET inhibitor savolitinib (AZD6094, HMPL-504) also improved the tumor growth inhibition substantially. At the end of the efficacy studies, CD31 and phosphorylation of EGFR, c-MET, protein kinase B (AKT) and extracellular signal-regulated kinase (ERK) were analyzed with immunohistochemistry and western blotting method in tumor tissues. The results suggested that the enhanced anti-tumor effect in combination therapy could be attributed to the simultaneous blockade of cell signaling in tumor cells (EGFR or c-MET) and VEGFR suppression in the tumor microenvironment.

Up-regulation of the immune inhibitory checkpoints induced by vascular endothelial growth factor ("VEGF") is one of the important mechanisms for tumor cells to escape immune surveillance. In a syngeneic murine tumor model, co-administration of fruquintinib and anti-Programmed death-ligand 1 ("PD-L1") antibody was found to provide improved anti-tumor effect compared to fruquintinib or anti-PD-L1 single agent alone. Studies to understand the mechanism responsible for the combination effect are underway.

All combinations with fruquintinib described above were well tolerated. The efficacy observed in these models suggested that simultaneous blockade of tumor angiogenesis and tumor cell signaling or immune evasion may be a promising approach in improving treatment outcomes.

Preclinical evaluation of sulfatinib, a novel angio-immuno kinase inhibitor targeting VEGFR, FGFR1 and CSF-1R kinases

Authors: Jinghong Zhou, Jun Ni, Min Cheng, Na Yang, Junqing Liang, Liang Ge, Wei Zhang, Jianxing Tang, Qiaoling Sun, Fu Li, Jia Hu, Dongxia Shi, Hongbo Chen, Jingwen Long, Junen Sun, Fang Yin, Xuelei Ge, Hong Jia, Feng Zhou, Yongxin Ren, Weiguo Qing and Weiguo Su

Both VEGFR and FGFR signaling pathways can mediate tumor angiogenesis. CSF-1R plays an important role on functions of macrophages. Recently, the roles in increasing tumor immune evasion of VEGFR, FGFR in regulation of T cells, tumor-associated macrophages ("TAMs") and myeloid-derived suppressor cells have been demonstrated. Therefore, blockade of tumor angiogenesis and tumor immune evasion by simultaneously targeting VEGFR, FGFR and CSF-1R kinases may represent a promising approach for anti-cancer therapy.

We report here the preclinical studies for sulfatinib (HMPL-012), a potent and highly selective small molecule tyrosine kinase inhibitor against VEGFR, FGFR1 and CSF-1R. Sulfatinib inhibited VEGFR1, 2, and 3, FGFR1 and CSF-1R kinases with IC_{50} s in a range of 1~24 nM, and it strongly blocked VEGF induced VEGFR2 phosphorylation in HEK293^{KDR} cells and colony-stimulating factor-1 stimulated CSF-1R phosphorylation in RAW264.7 cells with IC_{50} of 2 and 79 nM, respectively. Sulfatinib also attenuated VEGF or FGF stimulated HUVEC cells proliferation with $IC_{50} < 50$ nM. In animal studies, a single oral dosing of sulfatinib inhibited VEGF stimulated VEGFR2 phosphorylation in lung tissues of nude mice in an

exposure-dependent manner. Furthermore, elevation of FGF23 levels in plasma 24 hours post dosing suggested suppression of FGFR signaling. Sulfatinib demonstrated potent tumor growth inhibition in multiple human xenograft models and decreased CD31 expression remarkably, suggesting strong inhibition on angiogenesis through VEGFR and FGFR signaling. In a syngeneic murine colon cancer model CT-26, sulfatinib demonstrated moderate tumor growth inhibition after single agent treatment. Flow cytometry and immunohistochemistry analysis revealed an increase of CD8+ T cells and a significant reduction in TAMs, (CD163+ or F4/80+CD11b+CD45+) and CSF-1R+ TAMs in tumor tissue indicating strong effect on CSF-1R. Interestingly, combination of sulfatinib with a PD-L1 antibody resulted in enhanced anti-tumor effect. These results suggested that sulfatinib has a strong effect in modulating angiogenesis and cancer immunity.

In summary, sulfatinib is a novel angio-immuno kinase inhibitor targeting VEGFR, FGFR1 and CSF-1R kinases that could simultaneously block tumor angiogenesis and immune evasion. This unique feature seems to support sulfatinib as an attractive candidate for exploration of possible combinations with checkpoint inhibitors against various cancers. Sulfatinib is currently in multiple clinical trials including two Phase III trials against neuroendocrine tumors.

About Fruquintinib

Fruquintinib is a highly selective small molecule drug candidate that has been shown to inhibit VEGFR 24 hours a day via an oral dose, without known off-target toxicities. At an advanced stage, tumors secrete large amounts of VEGF, a protein ligand, to stimulate formation of excessive vasculature (angiogenesis) around the tumor to provide greater blood flow, oxygen, and nutrients to the tumor. VEGF and VEGFR play a pivotal role in tumor-related angiogenesis, and the inhibition of the VEGF/VEGFR pathway. This represents an important therapeutic strategy in blocking the development of new blood vessels essential for tumors to grow and invade.

Fruquintinib is currently under joint development in China by Chi-Med and its partner Lilly. In early March, Chi-Med and Lilly jointly announced top-line results from FRESCO, the Phase III pivotal registration trial of fruquintinib in 416 patients with locally advanced or metastatic CRC in China, who failed at least two prior chemotherapies, including fluoropyrimidine, oxaliplatin and irinotecan. The FRESCO trial met its primary endpoint of demonstrating a clinically meaningful and a statistically significant increase in OS in the intention-to-treat ("ITT") population of patients treated with fruquintinib plus best supportive care ("BSC") as compared to patients treated with placebo plus BSC. Chi-Med is currently preparing to submit an NDA for fruquintinib to the CFDA. In addition to OS, a statistically significant improvement in progression-free survival ("PFS"), a key secondary endpoint, was observed. The adverse events demonstrated in FRESCO did not identify any new or unexpected safety issues. Full detailed results are subject to ongoing analysis and are expected to be disclosed at an upcoming scientific meeting in mid-2017.

In addition to the FRESCO CRC trial, fruquintinib is being studied in China in a Phase III pivotal trial in NSCLC, known as FALUCA; and a Phase II study using fruquintinib combined with Iressa® (gefitinib) in the first-line setting for patients with advanced or metastatic NSCLC. Other studies currently being planned, and soon to be initiated, include a Phase III study in gastric cancer in combination with paclitaxel in China, new studies in the United States, and certain exploratory studies in combination with other oncology agents.

About Sulfatinib

Sulfatinib is an oral, novel angio-immunokinase inhibitor that selectively inhibits the tyrosine kinase activity associated with VEGFR, FGFR and CSF-1R, three key tyrosine kinase receptors involved in tumor angiogenesis and immune evasion. Inhibition of the VEGFR signaling pathway can act to stop angiogenesis, the growth of the vasculature around the tumor, and thereby starve the tumor of the nutrients and oxygen it needs to grow rapidly. Aberrant activation of the FGFR signaling pathway, which can be increased by anti-VEGFR therapy treatment, is shown to be associated with cancer progression by promoting tumor growth, angiogenesis and formation of the myeloid derived suppressor cells. Inhibition of the CSF-1R signaling pathway blocks the activation of tumor-associated macrophages, which are involved in suppressing immune responses against tumors.

Six sulfatinib clinical trials are underway in China and the United States, including two Phase III studies and one Phase II study in NET patients (SANET-p, SANET-ep and SANET-1), one Phase II study in thyroid cancer patients and one Phase II study in biliary tract cancer patients.

About Chi-Med

Chi-Med is an innovative biopharmaceutical company which researches, develops, manufactures and sells pharmaceuticals and healthcare products. Its Innovation Platform, Hutchison MediPharma Limited, 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 press release contains forward-looking statements within the meaning of the "safe harbor" provisions of the U.S. Private Securities Litigation Reform Act of 1995. These forward-looking statements reflect Chi-Med's current expectations regarding future events, including its expectations for the clinical development of fruquintinib or sulfatinib, plans to initiate clinical studies for fruquintinib or sulfatinib, 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 enrollment 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 drug candidates fruquintinib or sulfatinib to meet the primary or secondary endpoint of a study, to obtain regulatory approval in different jurisdictions, to gain commercial acceptance after obtaining regulatory approval, the potential market of fruquintinib or sulfatinib for a targeted indication and the sufficiency of funding. In addition, as certain studies rely on the use of Iressa® as a combination therapeutic with fruquintinib, such risks and uncertainties include assumptions regarding the safety, efficacy, supply and continued regulatory approval of Iressa®. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. For further discussion of these and other risks, see Chi-Med's filings with the U.S. Securities and Exchange Commission and on AIM. Chi-Med undertakes no obligation to update or revise the information contained in this press release, whether as a result of new information, future events or circumstances or otherwise.

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