Fruquintinib: further analyses from the FRESCO-2 study and exploratory combination studies

Fruquintinib is a highly selective and potent oral inhibitor of vascular endothelial growth factor receptor ("VEGFR")-1, -2 and -3. Fruquintinib has been generally well tolerated in patients to date and is being investigated as a single agent and in combination with other anti-cancer therapies. 13 presentations and publications, including several investigator-initiated-trials ("IITs"), are listed in the table below.

Additional FRESCO-2 analyses: New analyses from the FRESCO-2 multi-regional clinical trial (MRCT) are being presented. FRESCO-2 is a key study supporting ongoing and upcoming submissions to the U.S., European and Japanese regulatory authorities for the treatment of previously treated metastatic colorectal cancer ("CRC"). FRESCO-2 results were first presented at the European Society for Medical Oncology Congress 2022. These new analyses add to the understanding of fruquintinib efficacy by specific lines of therapy as well as adverse events of special interest ("AESI"). In subgroup analyses by prior lines of therapies up to six or more and by prior treatment with approved agents, fruquintinib improved overall survival ("OS") and progression free survival ("PFS") for all subgroups and prior therapies, consistent with those of the intent-to-treat ("ITT") population. Furthermore, during the study AESIs led to low rates of dose reduction (13.6% for patients who received fruquintinib vs 0.9% for patients who received placebo) and dose discontinuation (8.3% for patients who received fruquintinib vs 6.1% for patients who received placebo).

CRC real-world data: Results from a prospective, 3,005-patient Phase IV study to evaluate the safety of fruquintinib in real-world clinical practice in China are consistent with the fruquintinib safety profile observed in existing clinical studies, with no new or significant safety signals identified.

PD-1 combination in ccRCC: PFS results from an exploratory study of the fruquintinib and sintilimab (an anti-programmed cell death protein-1 ["PD-1"] antibody) combination in metastatic clear cell renal cell carcinoma ("ccRCC") are available with longer term follow-up. At data cut-off on November 30, 2022, median PFS was 15.9 months in 20 previously treated patients. Median PFS was not reached when results from this study were initially presented at the 2021 Chinese Society of Clinical Oncology Annual Meeting (data cut-off on August 31, 2021). No new safety signals were observed. A Phase II/III trial of fruquintinib in combination with sintilimab as second-line treatment for locally advanced or metastatic ccRCC was initiated in October 2022 (NCT05522231).

IIT in 2L MSS CRC: A number of IITs are being presented, including initial results of an IIT for fruquintinib in combination with investigator’s choice of chemotherapy in second-line metastatic CRC with microsatellite-stable (MSS) phenotype. At median follow up of 8.4 months, median PFS was not reached in 31 efficacy evaluable patients, disease control rate (DCR) was 90.3% and objective response rate (ORR) was 48.4%. Five patients received reduced doses of fruquintinib.

Surufatinib: exploratory results in combination with other agents

Surufatinib is a small-molecule inhibitor of VEGFR-1, -2 and -3, fibroblast growth factor receptor ("FGFR")-1 and colony-stimulating factor 1 receptor (CSF-1R). Seven related presentations and publications, including IITs, are listed in the table below.

PD-1 combinations: We conducted an open-label, multi-cohort, single-arm Phase II study of surufatinib plus toripalimab (an anti-PD-1 antibody) in several advanced solid tumors. We reported the results from the advanced thyroid cancer and endometrial cancer cohorts (NCT04169672). Amongst efficacy evaluable radioactive iodine-refractory differentiated thyroid cancer patients, median PFS was 10.9 months and median OS was not reached (median follow-up duration was 22.1 months). Amongst efficacy evaluable endometrial cancer patients, median PFS was 5.4 months and 12-month OS rate was 71.0% (median follow-up duration was 16.8 months). In both cohorts, the combination showed a tolerable safety profile.
**Combo IITs:** A number of IITs are being presented for surufatinib in combination with other agents, including chemotherapy as well as with camrelizumab (an anti-PD-1 antibody) plus different chemotherapy regimens.

Preliminary results in an ongoing IIT in treatment of patients with naïve metastatic pancreatic adenocarcinoma (PDAC) showed median PFS of 8.8 months in patients who received a combination of surufatinib, camrelizumab, nab-paclitaxel and S-1, compared to 5.8 months in patients who received gemcitabine in combination with nab-paclitaxel. Markers of immune cells were observed in an analysis of tissue samples from 13 (out of 20) patients who received S-1 in combination with surufatinib, camrelizumab and nab-paclitaxel. The combination safety profiles were manageable.

The IIT in previously treated CRC study completed the dose escalation phase of the study in 12 patients and enrolled a further 36 patients in the dose expansion phase of the study. The investigators found the combination of surufatinib with camrelizumab, irinotecan and GM-CSF to be well tolerated with a manageable safety profile. Median PFS was 7.2 months (95% CI 3.7-10.7).

The IIT in previously treated, advanced driver-gene negative, non-squamous, non-small cell lung cancer ("NSCLC") in combination with chemotherapy. This study complements Phase II results previously presented for the surufatinib and toripalimab combination in patients with treatment naïve advanced NSCLC with positive PD-L1 expression.

**HMP4-453: first in human results**

FGFRs regulate numerous cellular processes. Dysregulation of FGFR signaling due to receptor fusion, mutation or amplification is observed across multiple cancer types, making activated FGFRs an important therapeutic target. HMP4-453 is a highly potent and selective inhibitor of FGFR-1, -2, and -3. Preclinical data presented at the American Association for Cancer Research Annual Meeting 2023 (AACR 2023) showed that it has strong activity against FGFR-deregulated tumors, supporting investigation in patients with FGFR alterations (such as fusion and mutation) either as a single agent or in combination with PD-1 blockade.

Here we present first-in-human data for HMP4-453 in patients with previously treated advanced intrahepatic cholangiocarcinoma (IHCC) harboring FGFR2 fusions. A Phase II registration intent cohort is currently enrolling such patients (NCT04353375).

*Further details including the full abstracts are available at meetings.asco.org, as summarized below.*

### ABSTRACT PRESENTATION DETAILS

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<td>Fruquintinib</td>
<td>Arvind Dasari, MD Anderson Cancer Center</td>
<td>Abstract # 3604 Poster Session Gastrointestinal Cancer—Colorectal and Anal Monday, June 5, 2023, 8 am CDT, Hall A</td>
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<td>Subgroup analyses of safety and efficacy by number and types of prior lines of treatment in FRESCO-2, a global phase III study of fruquintinib in patients with refractory metastatic colorectal cancer</td>
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<td>Analysis of fruquintinib adverse events of special interest from phase 3 of the FRESCO-2 study</td>
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<td>Jin Li, Tongji University Shanghai East Hospital</td>
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<td>Fruquintinib plus sintilimab in patients with either treatment-naïve or previously first line treated metastatic clear-cell renal cell carcinoma (ccRCC): Results from a multicenter, single-arm phase 2 study</td>
<td>Dingwei Ye, Fudan University Shanghai Cancer Center</td>
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<td>Efficacy and safety of fruquintinib plus investigator's choice of chemotherapy as second-line therapy in metastatic colorectal cancer: A multicenter, single-arm phase 2 trial</td>
<td>Wensi Zhao, Renmin Hospital of Wuhan University</td>
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<td>Fruquintinib plus oxaliplatin combined with S-1 (SOX) as neoadjuvant therapy for locally advanced gastric adenocarcinoma (FRUTINEOGA): a multicenter, phase II study.</td>
<td>Liucheng Wu, Guangxi Medical University Cancer Hospital</td>
<td>Abstract # e16063 Publication Only Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary</td>
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the world, with its first three oncology drugs now approved and marketed in China. For more information, please visit: www.hutch-med.com or follow us on LinkedIn.

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 HUTCHMED’s current expectations regarding future events, including its expectations regarding the therapeutic potential of fruquintinib, surufatinib, and HMPL-453, the further clinical development for fruquintinib, surufatinib, and HMPL-453, its expectations as to whether any studies on fruquintinib, surufatinib and HMPL-453 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 and the 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 fruquintinib, surufatinib and HMPL-453, including as a combination therapy, to meet the primary or secondary endpoint of a study, to obtain regulatory approval in different jurisdictions and to gain commercial acceptance after obtaining regulatory approval; the potential market of fruquintinib, surufatinib and HMPL-453 for a targeted indication; the sufficiency of funding; and the impact of the COVID-19 pandemic on general economic, regulatory and political conditions. 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 HUTCHMED’s filings with the U.S. Securities and Exchange Commission, The Stock Exchange of Hong Kong Limited and on AIM. HUTCHMED 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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