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Press Release

HUTCHMED Highlights HMPL-A251 Data Presented at the AACR NCI EORTC International Conference on Molecular Targets and Cancer Therapeutics

- First investigational drug candidate using the HUTCHMED ATTC technology platform to create potent targeted therapy payloads while mitigating related toxicities -

- Unique, highly potent PI3K/PIKK inhibitor payload optimized to exploit antibody-conjugate advantages, with directed delivery and low plasma exposure of free payload -

- Preclinical data shows robust antitumor activity with synergistic and bystander killing effects -

Hong Kong, Shanghai & Florham Park, NJ - Thursday, October 23, 2025: HUTCHMED (China) Limited ("HUTCHMED") (Nasdaq/AIM:HCM; HKEX:13) today announces preclinical data for HMPL-A251 at the AACR NCI EORTC International Conference on Molecular Targets and Cancer Therapeutics, held October 22-26, 2025, in Boston, USA. HMPL-A251 is a first-in-class PI3K/AKT/mTOR ("PAM")-HER2 Antibody-Targeted Therapy Conjugate ("ATTC") comprising of a highly selective and potent PI3K/PIKK inhibitor payload linked to a humanized anti-HER2 IgG1 antibody, via a cleavable linker.

HER2 is a well-established therapeutic target. HER2 overexpression is found in a variety of cancer types and often associated with poor prognosis. As a key downstream signaling pathway of HER2, the PAM pathway contributes significantly to the resistance against HER2-targeting treatments when altered. HMPL-A251 is innovatively designed to leverage the synergy between HER2 targeting and PAM pathway inhibition to address limitations of traditional toxin-based antibody-drug conjugates ("ADCs") and standalone PAM inhibitors.

In vitro, the PI3K/PIKK inhibitor payload exhibited high potency, selectivity, and broad anti-tumor activity across a panel of 130 tumor cell lines. By conjugating this potent payload with an anti-HER2 antibody via a hydrophilic linker, the ATTC compound HMPL-A251, upon binding to the HER2-positive target cells, undergoes rapid internalization, lysosomal trafficking, payload release, and inhibition of PAM and PIKK signaling, inducing tumor cell apoptosis. HMPL-A251 demonstrated HER2-dependent antitumor activity *in vitro*, potently inhibiting HER2-positive tumor cell growth regardless of PAM pathway alterations, with moderately reduced activity in HER2-low, PAM-altered cell lines. HMPL-A251 also demonstrated a bystander effect on HER2-null cells when co-cultured with HER2-positive cells.

Unlike toxin-based ADCs, which often face challenges with toxicity related to their cytotoxic payloads, ATTCs are designed to prioritize tumor-specific delivery of a pathway-modulating payload, enhancing safety for long term use and enabling potential frontline combinations with chemotherapy. *In vivo*, HMPL-A251 demonstrated superior anti-tumor efficacy and tolerability as compared to the naked antibody and payload administered together. A single intravenous dose of HMPL-A251 induced tumor regression across multiple models including HER2-positive and HER2-low models with or without PAM alteration. Efficacy correlated strongly with payload concentration and target inhibition in tumor tissue. Notably, when benchmarked against T-DXd (trastuzumab deruxtecan, a HER2 directed ADC), HMPL-A251 achieved superior or comparable efficacy at equivalent doses in most tested models. Moreover, payload-based toxicities are expected to be low, as the plasma exposure of free payload was much lower than for HMPL-251, with a mass ratio of less than 1:500,000.

"We are excited to share the progress of HMPL-A251, the first candidate from our ATTC platform. It represents a potentially significant leap forward in addressing the limitations of toxin-based ADCs and narrow therapeutic window of systemic PAM inhibitors. By combining selective PI3K/PIKK inhibition with precise HER2 targeting, HMPL-A251 achieves potent antitumor effects while maintaining a favorable safety profile," said **Dr Michael Shi, Head of R&D and Chief Medical Officer of HUTCHMED**. "The compelling preclinical data presented underscore its potential to redefine treatment for a wide spectrum of cancers, and we are excited to advance HMPL-A251 as well as more ATTC drug candidates toward clinical trials."

HUTCHMED plans to initiate global clinical trials for HMPL-A251 around the end of 2025, followed by multiple global Investigational New Drug (IND) filings for more ATTC candidates in 2026.

About the ATTC platform

HUTCHMED's Antibody-Targeted Therapy Conjugate platform represents a next-generation approach to precision oncology, combining monoclonal antibodies with proprietary small-molecule inhibitor payloads to deliver dual mechanisms of action. Unlike traditional cytotoxin-based ADCs, ATTCs combine targeted therapies to achieve synergistic anti-tumor activity and durable responses in preclinical models, outperforming standalone antibody or small-molecule inhibitor components in efficacy and safety.

Built on over 20 years of targeted therapy expertise, the platform enables development of drug candidates for diverse cancer types. By leveraging antibody-guided delivery and tumor-specific payload release, ATTCs improve the accessibility to tumors and reduce off-tumor toxicity. This overcomes challenges of traditional small-molecule inhibitors, ensures safer long-term use, and supports combinations with chemotherapy and immunotherapy, unlocking potential for early-line treatments.

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About HUTCHMED

HUTCHMED (Nasdaq/AIM:HCM; HKEX:13) is an innovative, commercial-stage, biopharmaceutical company. It is committed to the discovery and global development and commercialization of targeted therapies and immunotherapies for the treatment of cancer and immunological diseases. Since inception it has focused on bringing drug candidates from in-house discovery to patients around the world, with its first three medicines marketed in China, the first of which is also approved around the world including in the US, Europe and Japan. For more information, please visit: www.hutchmed.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 US Private Securities Litigation Reform Act of 1995. These forward-looking statements reflect HUTCHMED's current expectations regarding future events, including but not limited to its expectations regarding the therapeutic potential of HMPL A251 and other drug candidates from the ATTC platform, the further clinical development for HMPL A251 and other drug candidates from the ATTC platform, its expectations as to whether any studies on HMPL A251 and other drug candidates from the ATTC platform 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. 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 HMPL A251 and other drug candidates from the ATTC platform, including as combination therapies, 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 markets of HMPL A251 other drug candidates from the ATTC platform for a targeted indication, 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. For further discussion of these and other risks, see HUTCHMED's filings with the US 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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