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ASCENTAGE PHARMA GROUP INTERNATIONAL

亞盛醫藥集團

(Incorporated in the Cayman Islands with limited liability)

(Stock Code: 6855)

Voluntary Announcement

Presentation by Ascentage Pharma of Results of Latest Preclinical Studies at 2021 American Association for Cancer Research (AACR) Annual Meeting which Demonstrate Potential of Multiple Combination Therapies

Ascentage Pharma Group International (the “**Company**” or “**Ascentage Pharma**”) is pleased to present the results of seven preclinical studies involving five of the Company’s novel drug candidates at the 2021 American Association for Cancer Research (AACR) Annual Meeting. These preclinical studies involve various tumor types and have signified the therapeutic potential of multiple combination therapies in cancer.

The AACR annual meeting is one of the world’s largest and longest-standing academic meetings in the field of cancer research. Covering some of the most cutting-edge advances in all the areas of oncology research and innovation, the annual event attracts tremendous focus from the global cancer research community.

Results from the seven preclinical studies of Ascentage Pharma selected for poster presentations at this year's AACR annual meeting include:

Candidate	Title	Abstract/ Poster Number
HQP1351	FMS-like tyrosine kinase 3 (FLT3) inhibition by olverembatinib (HQP1351) downregulates MCL-1 and synergizes with BCL-2 inhibitor APG-2575 in preclinical models of FLT3-mutant acute myeloid leukemia (AML)	1096
	ATP-site inhibitor olverembatinib, HQP1351, enhanced the effect of allosteric inhibitor on the resistance conferred by the compound mutations of BCR-ABL	1463
APG-2575	BCL-2 inhibitor APG-2575 and homoharringtonine (HHT) synergistically induces apoptosis and inhibits tumor growth in preclinical models of acute myeloid leukemia and myelodysplastic syndromes (AML/MDS)	981
	Inhibition of BCL-2 (by APG-2575) and CDK4/6 synergistically induces cell cycle arrest and apoptosis in ER ⁺ breast cancer	976
APG-1387	Therapeutic potential of inhibitor of apoptosis protein (IAP) inhibitor APG-1387 combined with DR5 agonist monoclonal antibody (mAb) CTB-006 in preclinical models of solid tumors	1924
APG-1252	Targeting BCL-xL addiction with APG-1252 (pelcitoclax) to overcome apoptotic blockade in neuroendocrine neoplasm (NEN)	984
APG-2449	Focal adhesion kinase (FAK) inhibitor APG-2449 sensitizes ovarian tumors to chemotherapy via CD44 downregulation	968

FMS-like tyrosine kinase 3 (FLT3) inhibition by olverembatinib (HQP1351) downregulates MCL-1 and synergizes with BCL-2 inhibitor APG-2575 in preclinical models of FLT3-mutant acute myeloid leukemia (AML)

➤ **Abstract/Poster Number: 1096**

➤ **Background**

AML accounts for 80% of acute leukemias in adults. FLT3 gene mutations are observed in approximately 30% of patients with AML and augur a poor prognosis. Despite antitumor effects of selective FLT3 inhibitors, resistance to these agents continues to pose a formidable clinical challenge in the treatment of AML. The expression of pro-survival protein BCL-2 is frequently dysregulated, and is one of the main reasons for conferring resistance to FLT3 inhibitors, in AML. In this study, we explored the combination of clinical stage multikinase inhibitor HQP1351 (which also targets FLT3) and BCL-2-selective inhibitor APG-2575 in preclinical models of FLT3-mutant AML.

➤ **Conclusion**

Taken together, our preclinical research data suggest that FLT3 inhibition by HQP1351 downregulates MCL-1 and synergizes with BCL-2 inhibitor APG-2575 to potentiate cellular apoptosis in FLT3-mutant AML. The results provide scientific rationale for clinical development of HQP1351 combined with APG-2575 in patients with FLT3-ITD-mutant AML.

ATP-site inhibitor olverembatinib, HQP1351, enhanced the effect of allosteric inhibitor on the resistance conferred by the compound mutations of BCR-ABL

➤ **Abstract/Poster Number: 1463**

➤ **Background**

Treatment with tyrosine kinase inhibitors (TKIs) directed against the ATP-binding site of BCR-ABL promotes recovery of Ph⁺ leukemia. However, emergence of gatekeeper mutation T315I and compound mutants confer resistance to these TKIs. The allosteric inhibitor, asciminib (ABL001), effectively inhibits BCR-ABL kinase through binding to the myristoyl-binding site. Combining asciminib with ponatinib can overcome only a subset of the resistance caused by BCR-ABL compound mutants. Olverembatinib (HQP1351) is a new generation TKI targeting BCR-ABL and currently in development for relapsed/refractory chronic myeloid leukemia (r/r CML). The purpose of this study is to evaluate whether a novel combination of olverembatinib and asciminib, targeting both ATP pocket and allosteric region of BCR-ABL protein, can promote the inhibitory effect on the kinase harboring compound mutations.

➤ **Conclusion**

Our results demonstrated that the combination of ATP binding site inhibitor olverembatinib and allosteric inhibitor have synergistic anti-tumor effect on tumor cells harboring single or compound mutations in BCR-ABL. This novel strategy may help to overcome the secondary compound mutations post the treatment with TKIs.

BCL-2 inhibitor APG-2575 and homoharringtonine (HHT) synergistically induces apoptosis and inhibits tumor growth in preclinical models of acute myeloid leukemia and myelodysplastic syndromes (AML/MDS)

➤ **Abstract/Poster Number: 981**

➤ **Background**

The AML treatment landscape has improved dramatically in the past decade, with improved objective response rates and overall survival after treatment with newly approved targeted therapies. BCL-2 inhibition combined with a hypomethylating agent or low-dose cytosine arabinoside (Ara-C) is also effective in previously untreated elderly patients who are not candidates for standard induction therapy. However, the effect of BCL-2 inhibition is commonly weakened when tumor cells upregulate antiapoptotic protein MCL-1 to escape apoptosis. Thus, combination therapy is introduced to suppress MCL-1 levels. HHT (omacetaxine mepesuccinate) has been widely used in Chinese patients with AML for 30 years. As an inhibitor of protein synthesis, HHT decreases MCL-1. This study investigated the effect of combining clinical stage BCL-2 selective inhibitor APG-2575 with HHT in AML and MDS cells, as well as murine xenograft tumor models.

➤ **Conclusion**

In summary, APG-2575 synergizes with HHT to potentiate antitumor activity in preclinical models of AML/MDS. HHT suppresses MCL-1 protein, preventing or abolishing formation of MCL-1:BIM, MCL-1:PUMA, and MCL-1:BAK complexes, and hence allowing prodeath proteins to fully engage in tumor cell apoptosis induction. Our results provide scientific rationale for clinical development of APG-2575 plus HHT.

Inhibition of BCL-2 (by APG-2575) and CDK4/6 synergistically induces cell cycle arrest and apoptosis in ER⁺ breast cancer

➤ **Abstract/Poster Number: 976**

➤ **Background**

Estrogen receptor positive (ER⁺)/human epidermal growth factor receptor 2 negative (HER2-) tumors represent the most common subset (about 75%) of all breast cancer cases. Combination treatment with endocrine therapy and a CDK4/6 inhibitor (CDK4/6i) is now the standard of care in early metastatic ER⁺ breast cancer. However, relapse or resistance to such combination therapy nearly inevitably occurs. Research shows that antiapoptotic protein BCL-2 is overexpressed in 80% of primary and metastatic ER⁺ breast cancer. Past research has shown that clinical-stage BCL-2 selective inhibitor APG-2575 enhances antitumor activity when combined with palbociclib in ER⁺ breast cancer xenograft models, including malignancies that are resistant to tamoxifen or progress after CDK4/6i treatment. We investigated mechanisms of action (MOAs) for synergistic effects of this combination.

➤ **Conclusion**

Taken together, palbociclib drives breast cancer cells into a senescent state, and APG-2575 potentiates this antitumor effect by inducing cellular apoptosis. BCL-2 selective inhibitor APG-2575 and CDK4/6i palbociclib-based therapy also causes cell cycle arrest, and both agents collaboratively induce apoptosis in the combination setting. Our data strengthens the scientific rationale for further clinical development of the BCL-2 selective inhibitor APG-2575 and its combination with CDK4/6i palbociclib-based therapy in patients with ER⁺/HER2- breast cancer.

Therapeutic potential of inhibitor of apoptosis protein (IAP) inhibitor APG-1387 combined with DR5 agonist monoclonal antibody (mAb) CTB-006 in preclinical models of solid tumors

➤ **Abstract/Poster Number: 1924**

➤ **Background**

TNF-related apoptosis-inducing ligand (TRAIL) receptor (DR4 or DR5) agonists are promising agents for cancer therapy because they induce apoptosis selectively in cancer cells. However, their clinical effect is hampered by either primary or acquired resistance in cancer cells. Second mitochondria-derived activator of caspase (SMAC) mimetics that antagonize the IAPs potently sensitize cancer cells to TRAIL-induced apoptosis in a caspase-8-dependent manner. We evaluated antitumor effects of small-molecule IAP antagonist APG-1387 combined with an agonist mouse mAb directed against TRAIL death receptor type 5 (DR5) termed CTB-006 in the preclinical setting. Both agents are in phase I/II clinical development for patients with solid tumors.

➤ **Conclusion**

In summary, our results suggest the synergistic antitumor activity and great potential of combination therapy with APG-1387 and CTB-006 for solid tumor therapy and deserves further clinical investigation.

Targeting BCL-xL addiction with APG-1252 (pelcitoclax) to overcome apoptotic blockade in neuroendocrine neoplasm (NEN)

➤ **Abstract/Poster Number: 984**

➤ **Background**

Current targeted therapies such as VEGFR inhibitor sunitinib and mTOR inhibitor everolimus extend progression-free survival (PFS) in patients with Grade 1 (G1) and G2 neuroendocrine tumors (NET), but the objective response rate remains low. The median PFS in patients with advanced neuroendocrine carcinoma (NEC) receiving platinum-based therapy is only 3 to 4 months. Hence, more effective therapy is needed to improve clinical outcomes. This study explored if BCL-2 family antideath proteins play a role in NEN tumorigenesis and whether clinical-stage dual BCL-2/BCL-xL inhibitor APG-1252 might overcome intrinsic apoptotic blockade in NEN.

➤ **Conclusion**

In summary, the results suggest that BCL-xL plays an important role in NEN. Cellular sensitivity to BCL-2/BCL-xL inhibitor APG-1252-M1 correlates with baseline BCL-xL complex levels. In NEN patient samples, MCL-1 was also highly expressed, implicating its potential negative regulatory effect on sensitivity to APG-1252. Concurrent expression of BCL-xL and MCL-1 proteins suggests that a combination treatment targeting both proteins might be more effective in NEN. Our findings inform development of a BCL-2/BCL-xL inhibitor for NEN therapy.

Focal adhesion kinase (FAK) inhibitor APG-2449 sensitizes ovarian tumors to chemotherapy via CD44 downregulation

➤ **Abstract/Poster Number: 968**

➤ **Background**

Ovarian cancer is one of the deadliest malignancies in women, and up to 70% of patients with epithelial ovarian cancer have FAK overexpression, amplification, or activation. FAK plays an important role in cellular migration, growth factor signaling, cell cycle progression, cellular survival and chemoresistance. This biomarker is also significantly associated with higher tumor stage, metastasis, and shorter overall survival in patients with ovarian cancer. Inhibition of FAK is therefore emerging as a promising treatment target. APG-2449 is a clinical stage FAK/ALK/ROS1 multikinase inhibitor. In this study we investigated antitumor activity of APG-2449 combined with standard-of-care chemotherapeutics in ovarian cancer in the preclinical setting.

➤ **Conclusion**

In summary, our data suggest that FAK inhibition by APG-2449 sensitizes ovarian tumors to chemotherapeutics in preclinical tumor models of ovarian cancer. The synergistic antitumor activity was mediated by downregulation of cancer stem cell populations. These findings encourage clinical development of APG-2449 in combination with chemotherapies for treatment of ovarian cancer.

Information on Ascentage Pharma

Ascentage Pharma is a China-based, globally focused, clinical-stage biotechnology company engaged in developing novel therapies for cancers, CHB (Chronic hepatitis B), and age-related diseases. On October 28, 2019, Ascentage Pharma became listed on the Main Board of The Stock Exchange of Hong Kong Limited with the stock code: 6855.HK.

Ascentage Pharma has its own platform for developing therapeutics that inhibit protein-protein interactions to restore apoptosis or programmed cell death. The company has built a pipeline of eight type I small molecule clinical drug candidates which have entered the clinical development stage, including novel, highly potent Bcl-2 inhibitors, as well as candidates aimed at IAP and MDM2-p53 pathways, and next-generation tyrosine kinase inhibitors (TKIs). Ascentage Pharma is also the only company in the world with active clinical programs targeting all key apoptosis regulators. The Company is conducting more than 40 Phase I/II clinical trials in China, the US and Australia. HQP1351, the Company's core drug candidate developed for the treatment of drug-resistant chronic myeloid leukemia (CML), has been granted an Orphan Drug Designation (ODD) and a Fast Track Designation (FTD) by the US FDA, and a New Drug Application (NDA) for the drug candidate has been submitted and subsequently granted Priority Review by the Center for Drug Evaluation (CDE) in China. As at the date of this announcement, Ascentage Pharma has obtained a total of eleven ODDs from the US FDA for four of the Company's investigational drug candidates.

Cautionary Statement required by Rule 18A.05 of the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited: We cannot guarantee that we will be able to obtain further approval for, or ultimately market, HQP1351, APG-2575, APG-1387, APG-1252 and APG-2449 successfully.

By order of the Board
Ascentage Pharma Group International
Dr. Yang Dajun
Chairman and Executive Director

Suzhou, People's Republic of China, April 13, 2021

As at the date of this announcement, the Board of Directors of the Company comprises Dr. Yang Dajun as Chairman and executive Director, Dr. Wang Shaomeng, Dr. Tian Yuan, Dr. Lu Simon Dazhong and Mr. Liu Qian as non-executive Directors, and Mr. Ye Changqing, Dr. Yin Zheng, Mr. Ren Wei and Dr. David Sidransky as independent non-executive Directors.