亞盛醫藥
Ascentage Pharma

ASCENTAGE PHARMA GROUP INTERNATIONAL
亞盛醫藥集團

(Incorporated in the Cayman Islands with limited liability)
(Stock Code: 6855)

Voluntary Announcement

Ascentage Pharma Presents Latest Results from Six Preclinical Studies at AACR Annual Meeting 2022

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that it has presented the latest results from six preclinical studies of the Company's five investigational drug candidates: the Bcl-2 inhibitor lisaftoclax (APG-2575), the MDM2-p53 inhibitor alrizomadlin (APG-115), two key candidates in the Company's apoptosis-targeted pipeline, as well as the FAK inhibitor APG-2449, the EED inhibitor APG-5918 and the KRAS inhibitor APG-1842, at the 2022 American Association for Cancer Research (AACR) Annual Meeting.

The AACR Annual Meeting is one of the world's largest and longest-standing scientific gatherings in the field of cancer research. Covering the cutting-edge advances in all the areas of cancer research and innovation, the annual event attracts tremendous interest from the global cancer research community.

The details of these posters presented by Ascentage Pharma at AACR 2022 are as follows:

Co-targeting MDM2-p53 and BCL-2 apoptosis pathways overcomes resistance conferred by acquired BCL-2 gene mutations in preclinical models

Abstract Number: 3964

Introduction:

The BCL-2 inhibitor venetoclax, although efficacious in patients with chronic lymphocytic leukemia, meets significant resistance in a large number of patients due to acquired BCL-2 gene mutations. Among acquired mutations, those proximal to BH3 binding motifs (e.g., G101V, D103E, and V156D) have the most significant impact on BCL-2 binding to BH3-only pro-death proteins and BH3 mimetics (e.g., venetoclax). Hence, it is important to identify novel therapeutics that address this emerging unmet need.

Conclusions:

Our study demonstrates, APG-115 (alrizomadlin) combined with APG-2575 (lisaftoclax) synergistically inhibited the proliferation of RS4:11-BCL-2 mutant cell lines and the growth of cell-derived xenografts in vivo. Co-targeting BCL-2 and MDM2-p53 apoptosis pathways represents a new and effective strategy to overcome drug resistance conferred by clinically BCL-2 gene mutations.

Inhibition of MDM2-p53 interaction by alrizomadlin (APG-115) induces pyroptotic cell death in gasdermin E (GSDME)-expressing cancer cells

Abstract Number: 2998

Introduction:

The mouse double minute-2 (MDM2)-p53 inhibitor APG-115 (alrizomadlin) is an investigational agent known to induce apoptosis of TP53-wild type cancer cells (Aguilar et al, J Med Chem 2017). Emerging evidence suggests that activation of p53 by alrizomadlin also promotes antitumor immunity in the tumor microenvironment (Fang et al, JITC 2019; Zhou et al, Nat Immunol 2021), but the links between these processes are not yet completely understood. Pyroptosis refers to inflammatory programmed cell death. Central to this process is the family of gasdermins, which can form pores in cell plasma membranes, resulting in lysis and release of immune stimulants. In cells expressing these proteins, GSDME can be cleaved by caspase-3, which converts noninflammatory apoptosis to pyroptosis (Zhang et al, Nature 2020). In this context, caspase-3/GSDME appears to represent a switch between apoptosis and pyroptosis. Given that alrizomadlin elicits its apoptogenic activity primarily by activating caspase-3, we hypothesized that the MDM2-p53 inhibitor might also induce pyroptosis in GSDME-expressing cells by cleaving caspases.

Conclusions:

Our study demonstrates that, in addition to apoptosis, MDM2-p53 inhibitor APG-115 induces caspase-mediated pyroptosis in GSDME-expressing cancer cells. In this study, we reveal for the first time that apoptosis-inducing, APG-115 induces both apoptosis and pyroptosis in GSDME-expressing cancer cells. GSDME-dependent pyroptosis is a previously unrecognized mechanism of action for APG-115 to exert antitumor immunity, with potentially important implications for clinical development of therapy involving MDM2-p53 inhibition.

MDM2 inhibitor alrizomadlin (APG-115) stabilizes p53 and synergizes with proteasome inhibitors in multiple myeloma

Abstract Number: 5439

Introduction:

Multiple myeloma (MM) accounts for about 2% of all cancers and 18% of all hematologic malignancies in the US. Recent therapeutic advances (e.g., immunomodulators, proteasome inhibitors, monoclonal antibodies) have improved outcomes, but MM inevitably relapses and is considered incurable. Genomic analysis shows that the TP53 gene encoding tumor suppressor protein p53 is infrequently mutated in patients with MM, of whom about 82% retain wildtype (WT) TP53. Mouse double minute 2 (MDM2) is an E3 ubiquitin ligase that inhibits p53 via proteasome degradation. Proteasome inhibitors might help to stabilize p53 and synergize with MDM2 inhibitors. Therefore, MDM2 inhibitors that activate p53 might constitute an attractive pharmacologic approach to MM. APG-115 is an investigational, novel small molecule targeting the p53/MDM2 interaction and is in clinical development for solid and hematologic cancers. This study aimed to evaluate whether APG-115 can potentiate the antitumor effects of proteasome inhibitors in MM.

Conclusions:

The results demonstrate that the combination of MDM2 inhibitor APG-115 and proteasome inhibitors have synergistic antitumor effects on MM tumors harboring WT TP53 in animal models. These data warrant clinical studies to test this novel therapeutic option for patients with refractory MM.

FAK inhibitor APG-2449 and CDK4/6 inhibitor palbociclib synergistically suppress mesothelioma tumor growth via autophagy induction

Abstract Number: 2563

Introduction:

Malignant mesothelioma is a rare but highly lethal malignancy, with a 5-year survival rate of less than 10%. Among the most common genomic abnormalities are alterations of cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) and neurofibromin 2 (NF2). Mesothelioma cells lacking expression of CDKN2A/B or NF2 are reported to be sensitive to CDK4/6 or focal adhesion kinase (FAK) inhibition. In this study, APG-2449 as a clinical stage FAK/ALK/ROS1 multi-kinase inhibitor combined with CDK4/6 inhibitor palbociclib demonstrated anti-tumor activity.

Conclusions:

These results demonstrate that the combination of palbociclib and APG-2449 synergistically inhibits tumor growth in mesothelioma and such effect is mediated by induced autophagy and enhanced cellular senescence. The preclinical study suggests that APG-2449 combined with CDK4/6 inhibitors may have therapeutic potential in mesothelioma and may warrant future clinical development.

Preclinical development of embryonic ectoderm development (EED) inhibitor APG-5918/EEDi-5273 for cancer therapy

Abstract Number: 3939

Introduction:

Three core components constitute the polycomb repressive complex 2 (PRC2), a multiprotein complex that catalyzes the methylation of histone H3 at lysine 27 (H3K27me3): enhancer of zeste homolog 2 (EZH2), embryonic ectoderm development (EED) and suppressor of zeste 12 protein homolog (SUZ12). Dysregulated function of PRC2 has been implicated in the development of a variety of cancer types. With the use of tazemetostat, an EZH2 inhibitor, inhibition of PRC2 functions has been proven to be a successful cancer therapeutic strategy. Nevertheless, the activity of an EZH2 inhibitor might be compensated due to acquired resistance through secondary mutations in EZH2 or its paralog EZH1. Because binding of EED with trimethylated H3K27 (H3K27me3) is the prerequisite for the activation of the methyltransferase activity of EZH2, allosterically targeting EED is emerging as a novel approach to inhibit PRC2. APG-5918/EEDi-5273 has been reported as a novel, bioactive, and potent EED inhibitor. In this study, we further characterized APG-5918 for cancer therapy in a preclinical setting.

Conclusions:

APG-5918 was thoroughly characterized in the preclinical stage, with potent biochemical binding activity to EED protein, in vitro anti-proliferatively activity, and in vivo antitumor activities. APG-5918 showed definitive in vitro and in vivo target engagement and on-target antitumor activity. APG-5918 demonstrated strong PD/PK correlation in mice bearing KARPAS-422 xenograft tumors. APG-5918 appeared to be similar or more potent than MAK683, an EED inhibitor under clinical development, in terms of biochemical, in vitro, and in vivo activities. In summary, our results suggest potential utility of APG-5918 in cancer therapy and it deserves further clinical investigation.

Development of covalent $KRAS^{G12C}$ inhibitor APG-1842 for the treatment of solid tumors

Abstract Number: 2664

Introduction:

The KRAS gene is frequently mutated in human cancers, and the $KRAS^{G12C}$ mutation occurs in approximately 13% of non-small-cell lung cancers (NSCLCs) and in 1% to 3% of colorectal cancers and other solid tumors. $KRAS^{G12C}$ small molecule inhibitors, AMG510 and MRTX849, have been investigated as treatment options for solid tumors with the $KRAS^{G12C}$ mutation. In this study, APG-1842 was characterized as a potent, selective, and covalent KRASG12C inhibitor with demonstrated inhibition on KRAS-dependent signaling and demonstrated antitumor activity in $KRAS^{G12C}$ mutant cells and mouse tumor models.

Conclusions:

Collectively, these results demonstrate that APG-1842 is a potent, bioavailable, and highly selective $KRAS^{G12C}$ inhibitor. Our data provide the preclinical evidence for clinical development of APG-1842 in patients with $KRAS^{G12C}$-mutant solid tumors.

About 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, and dual Bcl-2/Bcl-xL 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 three known classes of key apoptosis regulators. The Company is conducting more than 50 Phase I/II clinical trials in China, the US, Australia and Europe. Olverembatinib, the Company's core drug candidate developed for the treatment of drug-resistant chronic myeloid leukemia (CML), was granted Priority Review status and a Breakthrough Therapy Designation (BTD) by the Center for Drug Evaluation (CDE) of China National Medical Products Administration (NMPA), and is already approved for the indication. In addition, Olverembatinib has also been granted an Orphan Drug Designation (ODD) and a Fast Track Designation (FTD) by the US FDA, and an Orphan Designation by the EU. As at the date of this announcement, Ascentage Pharma

has obtained a total of 15 ODDs from the US FDA and 1 ODD from the EU for four of the Company's investigational drug candidates. The Company has been designated for multiple major national R&D projects in China, including five Major New Drug Development Projects, one Enterprise Innovative Drug Incubator Base status, four Innovative Drug Research and Development Programs, and one Major Project for the Prevention and Treatment of Infectious Diseases.

Leveraging its robust research and development capabilities, Ascentage Pharma has built a portfolio of global intellectual property rights, and entered into global partnerships with numerous leading biotechnology and pharmaceutical companies and research institutes such as UNITY Biotechnology, MD Anderson Cancer Center, Mayo Clinic, Dana-Farber Cancer Institute, MSD, and AstraZeneca. The Company has built a global and talented team with experience in the research and development of innovative drugs and clinical development, and is setting up its commercial manufacturing and sales and marketing teams with high standards. Ascentage Pharma aims to continuously strengthen its research and development capabilities and accelerate the clinical development progress of its product pipeline to fulfil its mission of 'addressing unmet clinical needs of patients in China and around the world' for the benefit of more patients.

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, APG-2575, APG-115, APG-2449, APG-5918 and APG-1842 successfully.

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

Suzhou, People's Republic of China, April 14, 2022

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.