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 RESULTS FROM THREE STUDIES AT 2024 AMERICAN ASSOCIATION OF CANCER RESEARCH ANNUAL MEETING

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that it released the latest results from three preclinical studies of its novel drug candidates olverembatinib (HQP1351), MDM2-p53 inhibitor alrizomadlin (APG-115), FAK/ALK/ROS1 tyrosine kinase inhibitor APG-2449, and embryonic ectoderm development (EED) inhibitor APG-5918, at the 2024 American Association of Cancer Research Annual Meeting (AACR 2024).

The details of these three preclinical studies of Ascentage Pharma are as follows:

Olverembatinib, a novel multikinase inhibitor, demonstrates superior antitumor activity in succinate dehydrogenase (SDH)-deficient neoplasms

- Abstract number: 1971
- Time: Monday, April 8, 2024, 9:00 AM – 12:30 PM (Pacific Time)

Introduction:

- Succinate dehydrogenase (SDH) – deficient (dSDH) neoplasms are identified by the loss of immunohistochemical expression of SDHB due to the bi-allelic inactivation of any of the four components of mitochondrial SDH complex (SDH A-D).
- Succinate accumulation, due to SDH deficiency, are involved in the tumorigenesis in different types of cancers including gastrointestinal stromal tumor (GIST), paraganglioma, pheochromocytoma, renal cell carcinoma, pituitary adenomas, and pancreatic neuroendocrine tumors.
- The prognosis of patients with dSDH neoplasia, especially GIST, is poor and approved tyrosine kinase inhibitors (TKIs) have limited efficacy. There is a high unmet medical need for these patients.

- Olverembatinib, a novel multi-kinase inhibitor, targets a broad spectrum of kinases and has demonstrated promising efficacy in dSDH GIST patients in an ongoing phase I clinical trial. In this study, we assessed antitumor effects of olverembatinib in preclinical models of dSDH cancers, dSDH GIST primary tumor cells, and explored potential mechanisms of action (MOA).

Conclusions:

- Olverembatinib showed superior anti-tumor activity in dSDH cell lines *in vitro* and human dSDH GIST primary tumor cells *ex vivo*.

- Olverembatinib, as a multi-target kinase inhibitor, exerted antitumor effects by modulating multiple signal pathways including hypoxia, angiogenesis, apoptosis, proliferation, and survival, which are involved in tumorigenesis of dSDH cancers.

- Olverembatinib demonstrated more potent *in vivo* antitumor activity in mice bearing PC12#5F7 (SDHB KD) xenograft tumors than other TKIs. Western blot analysis in tumor tissues collected from mice further confirmed the modulation of the signal pathways by olverembatinib observed in cell lines.

- In summary, our results provide the rationale for the future clinical development of olverembatinib in dSDH cancers.

Embryonic ectoderm development (EED) inhibitor APG-5918 (EEDi-5273) and MDM2 inhibitor alrizomadlin (APG-115) synergistically inhibit tumor growth in preclinical models of prostate cancer (PCa)

- Abstract number: 3223

- Time: Monday, April 8, 2024, 1:30 PM – 5:00 PM (Pacific Time)

Introduction:

- Prostate cancer (PCa) is one of the most frequently diagnosed malignancies among elderly males. Androgen deprivation therapy (ADT) with or without androgen receptor (AR) inhibitors is widely used as initial treatment for advanced PCa. However, most ADT-treated patients eventually develop castration-resistant prostate cancer (CRPC), which is in urgent need of novel therapies.

- Polycomb repressive complexes 2 (PRC2) dysregulation is common in PCa and correlates with poor prognosis. PRC2 mediates histone H3 lysine 27 tri-methylation (H3K27me3), a repressive epigenetic marker for gene transcription. Embryonic Ectoderm Development (EED), a PRC2 core component, is crucial for histone methyltransferase activity through direct binding to H3K27me3.

- MDM2, a negative regulator of p53, is frequently amplified or overexpressed in PCa, and associated with poor clinical outcomes and metastasis.

- The aim of this study was to evaluate antitumor activity and molecular mechanisms of the clinical stage EED inhibitor APG-5918/EEDi-5273 and MDM2 selective inhibitor alrizomadlin (APG-115) in PCa preclinical models.

Conclusions:

- In PCa preclinical models, the combination of APG-5918 and alrizomadlin synergistically inhibited cellular proliferation and induced cellular apoptosis.

- APG-5918 in combination with alrizomadlin synergistically enhanced antitumor activity in PCa xenograft models *in vivo*.

- Mechanistically, PD analysis revealed that APG-5918 downregulated the oncogenic DNA methylation factors (UHRF1, DNMT1) and histone methylation marker H3K27me3. Alrizomadlin markedly downregulated UHRF1 and DNMT1, and upregulated p53 and p21 expression. Combined treatment further enhanced downregulation of DNMT1, UHRF1, cell cycle pathway proteins (pRb, CDK6), antiapoptotic protein MCL-1, and synergistically increased cleavage of PARP-1, a marker of apoptosis.

- Therefore, our findings provide a scientific rationale for the future clinical development of APG-5918 and alrizomadlin for treating patients with PCa.

APG-2449, a novel focal adhesion kinase (FAK) inhibitor, inhibits metastasis and enhances the antitumor efficacy of PEGylated liposome doxorubicin (PLD) in epithelial ovarian cancer (EOC)

- Abstract number: 4569

- Time: Tuesday, April 9, 2024, 9:00 AM – 12:30 PM (Pacific Time)

Introduction:

- Ovarian cancer is among the leading causes of cancer-related death in women and most cases are diagnosed at later stages with distant metastasis.

- FAK overexpression or activation occurs in a substantial proportion of epithelial ovarian cancer (EOC) and is predictive of poor clinical outcomes.

- FAK plays an important role in cell migration and chemoresistance, rendering FAK inhibition a promising treatment approach to reduce metastasis of tumor cells and sensitize them to chemotherapy. FAK is therefore emerging as a potential treatment target.

- The aim of this study was to evaluate the antitumor efficacy of investigational APG-2449, a novel FAK inhibitor, combined with PLD, a commonly used chemotherapy, in relapsed or refractory ovarian cancer.

Conclusions:

- APG-2449 combined with doxorubicin showed synergistic antiproliferative effects in both platinum-resistant and platinum-sensitive ovarian cancer cell lines.

- FAK inhibition via APG-2449 alone attenuated migration of ovarian cancer cells in a dose-dependent manner.

- APG-2449 in combination with PLD showed enhanced antitumor activity in platinum-resistant OVCAR-3 ovarian cancer CDX model.

- The combination regimen can prolong ascites-free and survival times in the ID8-Luc peritoneal syngeneic model.

- These promising results support the future clinical development of this combination treatment for ovarian cancer.

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

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

Suzhou, People's Republic of China, April 8, 2024

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 and Dr. Lu Simon Dazhong as non-executive Directors, and Mr. Ye Changqing, Dr. Yin Zheng, Mr. Ren Wei and Dr. David Sidransky as independent non-executive Directors.