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CStone registers for Phase I trial of CDK4/6 inhibitor CS3002 in Australia

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An open-label, multi-dose, dose-escalation, and dose-expansion Phase I clinical study designed to evaluate the safety, tolerability, pharmacokinetics, and anti-tumour efficacy of CS3002 in patients with advanced solid tumours

CStone Pharmaceuticals, on 23 August 2019, announced that the Company has recently received ethics approval from the Human Research Ethics Committee in Australia for the Phase I clinical trial of CS3002, and Australia's Therapeutic Goods Administration (TGA) has acknowledged the electronic Clinical Trial Notification (eCTN) the Company submitted for the trial. This clinical trial is an open-label, multi-dose, dose-escalation, and dose-expansion Phase I clinical study designed to evaluate the safety, tolerability, pharmacokinetics, and anti-tumour efficacy of CS3002 in patients with advanced solid tumours.

Being developed by CStone, CS3002 is a selective inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4/6). Inducing cell cycle arrest of tumour cells through the selective inhibition of CDK4/6, CS3002 has demonstrated the high therapeutic potential for combination with endocrine therapy or immune checkpoint inhibitor therapy in various solid tumours. At present, three CDK4/6 inhibitors have been approved by the U.S. FDA. However, in China, palbociclib is the only approved CDK4/6 inhibitor, indicated for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negatives (HER2-) advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women.

Preclinical studies have revealed that CS3002's *in vivo* and *in vitro* activities are comparable to that of palbociclib's. In mouse models, CS3002 combined with PD-1 monoclonal antibody therapy or endocrine therapy has shown improved tumour-suppressing activities compared to monotherapies. In addition, CS3002 has also demonstrated potentially favourable safety and tolerability profiles.

Dr Frank Jiang, Chairman and CEO of CStone, commented: "Currently, there are several CDK4/6 inhibitors that are either approved or in clinical development in the world. However, options in this class of therapies available to Chinese patients remain very limited and no domestically developed CDK4/6 inhibitor has been approved. I am pleased that we are about to initiate the Phase I trial on CS3002 in Australia. We will accelerate our work in obtaining its clinical trial approval in China and actively explore CS3002's application in the treatment of various tumour types and different combination therapies. We hope CS3002 will become a new effective treatment option benefiting Chinese patients."

Dr Jon Wang, CStone's Chief Scientific Officer, noted: "The aberrant activation CDK4/6 was observed across various tumour types, suggesting CS3002's potential utility in the treatment of breast cancer and a variety of other solid tumours. Recent studies have shown that, in addition to inducing cell cycle arrests, CDK4/6 inhibitors also have the effects of strengthening anti-tumour immunity and modulating the tumour microenvironment. These discoveries provide the foundation for a new approach in cancer treatment, which is the combination of CDK4/6 inhibitors and immunotherapies. We are hopeful that the clinical trial on CS3002 in Australia will be carried out successfully."

CS3002 is a new generation of well-tolerated and highly selective CDK4/6 inhibitor developed by CStone.CDK4/6 inhibitors are the cyclin-dependent kinases that play a crucial role in the regulation of cell cycle progression from the first Growth phase (G1 phase) to the Synthesis phase (S phase). Upon activation of the cell proliferation signal, cyclin D protein binds to CDK4/6. The cyclin D–CDK4/6 complex then phosphorylates downstream retinoblastoma (Rb) protein, resulting in the aberrant proliferative signalling in the CDK4/6 pathway that drives the cell cycle progression from the G1 phase to the S phase. Aberrant CDK activity is a common feature of most cancer types. CDK4/6 inhibitors could suppress the activities of CDK4/6 and the phosphorylation of Rb protein, thereby achieving the suppression of tumour cell growth by interrupting the cell cycle transition from the G1 phase to the S phase. The commonality of aberrant cyclin D–CDK4/6–INK4–Rb pathway signalling in tumour cells suggests CDK4/6 inhibitors' potential application in strengthening anti-tumour immunity and CDK4/6 inhibitors' promising potential for the treatment of various solid tumours and synergistic combination with immuno-oncology therapies.