SINO BIOPHARMACEUTICAL LIMITED
中國生物製藥有限公司

(Incorporated in the Cayman Islands with limited liability)
Website: www.sinobiopharm.com
(Stock code: 1177)

VOLUNTARY ANNOUNCEMENT
DATA OF 6 STUDIES REGARDING "ANLOTINIB HYDROCHLORIDE CAPSULES", "TQB2916 (CD40 AGONIST)" AND "FHND6091 (PROTEASOME INHIBITOR)" WERE PRESENTED AT 2024 AACR

The board of directors (the "**Board**") of the Sino Biopharmaceutical Limited (the "**Company**", together with its subsidiaries, the "**Group**") announced that three innovative drugs "Anlotinib Hydrochloride Capsules", "TQB2916 (CD40 agonist)" and "FHND6091 (Proteasome inhibitor)" developed by the Group were presented at the Annual Meeting 2024 of American Association for Cancer Research ("AACR") for their 6 study results.

Clinical studies

1. **Anlotinib: gastrointestinal tumor**
   No.: CT213/13

   Title of abstract: Anlotinib plus chemotherapy as first-line therapy for gastrointestinal tumor patients with unresectable liver metastasis: Updated results from a multi-cohort, multi-center phase II trial ALTER-G-001-cohort C

   Abstract: ALTER-G-001 is a multi-cohort, multi-center phase II study. The updated results of cohort C was presented in this meeting. In cohort C, patients received therapy of anlotinib (12mg, po, qd, d1-14, q3w) plus standard chemotherapy for 6 cycles of treatment (3 weeks per cycle). If liver metastases did not convert to resectable by imaging assessment, patients with efficacy assessed as complete remission (CR)/partial remission (PR)/stable disease (SD) after 6 courses of treatment were maintained on maintenance therapy with anlotinib in combination with metronomic capecitabine (500 mg, po, bid, d1-21, q3w) until PD or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints were progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DoR), radical resection rate for LMs, and safety.

Results: As of 13 November 2023, 41 patients were enrolled in cohort C, including those with pancreatic cancer (PC, n=29), gastric cancer (GC, n=6), biliary tract cancer (BTC, n=5), duodenal cancer (n=1). After induction therapy, 4 patients (1 PC, 2GC, 1 BTC) received surgical resection. Of 38 evaluable patients in cohort C, ORR was 42.1%, DCR was 86.8% (16 had partial response (PR), 17 had stable disease (SD) and 14 SD with reduced tumor size). Of 26 evaluable pancreatic cancer patients, ORR and DCR were 42.3% and 88.5% respectively. Median depth of remission (DpR) in PR patients was 52.1%; median DOR was 4.1 months (95%CI: 3.5-4.6) and median PFS was 5.8 months (95%CI: 5.2-6.3), median TTR was 1.7 months (95%CI: 0.8-3.5). The ≥ grade 3 TEAEs (53.7%) mainly included neutropenia (19.5%), white blood cell decreased (14.6%), and blood platelet decreased (9.8%).

The study showed that, anlotinib plus chemotherapy as first-line treatment has shown promising response and maybe a favorable option for advanced LMs GI tumors, especially for pancreatic cancer.

2. Anlotinib: small cell lung cancer

No.:5098/20

Title of abstract: Second-line treatment outcomes in Extensive Stage Small Cell Lung Cancer (ES-SCLC) patients after first-line immuno-chemotherapy

Abstract: First-line immune checkpoint inhibitors (ICIs) has significantly improved overall survival (OS) of ES-SCLC. However, second-line treatment options are still controversial with limited overall survival. This study aims to evaluate the data of treatment of different second-line regimens for relapsed ES-SCLC after first-line immuno-chemotherapy. We retrospectively reviewed 96 ES-SCLC patients receiving first-line immuno-chemotherapy in Cancer Hospital Chinese Academy of Medical Sciences, from January 2019 to December 2022. Clinical data were collected from electronic medical records. The clinical outcomes, including ORR, PFS and OS were assessed by Kaplan-Meier method and standard log-rank test.

Results: From 4 January 2019 to 18 December 2022, a total of 96 ES-SCLC patients received first-line immuno-chemotherapy and 49 of them went through second-line treatment in our center. Patient characteristics were listed as follows: median age 63 (31-79), male 76 (79.2%), heavy smoker 59 (61.5%), liver metastasis 40 (41.7%), brain metastasis 33 (34.4%) and refractory recurrence 58 (60.4%). Second-line treatments included immunotherapy crossover and combination with chemotherapy (n=40), anlotinib with or without chemotherapy (n=5), chemotherapy alone (n=4). ORR of the whole group in the second-line setting was 22.4%. Median PFS was 3.23 months (95%CI: 1.96-4.50). Cross-line immunotherapy failed to improved survival for relapsed ES-SCLC compared with those without ICIs (mPFS 3.23 vs. 3.13m, p=0.829). Anlotinib based treatment showed numerically superior PFS for relapsed SCLC compared with those without anlotinib therapy (mPFS 6.00 vs. 3.13m, p=0.089).

This retrospective study indicated cross-line ICIs failure to improve clinical outcome for relapsed ES-SCLC, and implied the potential benefits of anlotinib in second-line setting.

3. TQB2916: advanced malignancies

No.: CT192/20

Title of abstract: A first-in-human phase I study of TQB2916, a novel CD40 agonist antibody for advanced malignancies

Abstract: For the study, Bayesian optimal interval (BOIN) design was used to determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D).

Results: From April 2022 to November 2023, 18 patients with solid tumors and 2 with lymphoma were treated with TQB2916 monotherapy until PD or unacceptable toxicity. The results of the phase I clinical study showed that: TQB2916 pharmacokinetics were well-behaved with increasing exposure dose-proportionally and no accumulation occurred after repeated dosing; dose-dependent occupancy of CD40 was detected of 0.5 mg and above doses. Reduction in peripheral B cells and increasing in cytokines secretion were also observed. Of 16 evaluable patients, 3 of them achieved SD as per iRECIST and LYRIC standards with the longest subjects in group 3.7 months. Three dose limiting toxicities (DLTs) were observed: one with grade 3 pneumonia and one with grade 4 lipase/amylase increase in the 400 mg cohort; one with grade 3 pancreatitis in the 300 mg cohort. The most common TRAEs were lipase increase, amylase increase, lymphocyte count decrease, alanine aminotransferase (ALT) increase, alkaline phosphatase (ALP) increase, aspartate aminotransferase (AST) increase, hypoalbuminemia, and anorexia. Most of TRAEs were of grade 1 or grade 2 and manageable.

The study showed that: TQB2916 can in combination with CD40 to increases cytokine release, activates immunity and acts as an anti-tumor agent. 200 mg was determined as the preliminary expansion dose, and studies of TQB2916 in combination with other anti-cancer therapies are ongoing.

4. FHND6091: cholangiocarcinoma

No.: 7271/8

Title of abstract: Proteasome inhibitor FHND6091: A potent oral therapeutic candidate for PTEN-Deficient Cholangiocarcinoma

Abstract: In the field of treatment of cholangiocarcinoma (CCA), FHND6091, characterized by its irreversibility, high potency and oral bioavailability, becoming a clinical breakthrough oral drug candidate. The tumor suppressor gene PTEN is frequently altered in more than 50% of CCA clinical specimens. PTEN deficiency enhances proteasome subunit expression and proteasome proteolytic activity, and facilitates the potential therapeutic efficacy of proteasome inhibitors in CCA. Following a series of in vitro and in vivo evaluations, including enzyme activity and cellular activity testing, as well as CCA PDX model and tissue distribution studies, the pharmacological properties of FHND6091 were fully validated.

About FHND6091: FHND6091 has been approved for clinical trials by the National Medical Products Administration of China in February 2021 and March 2024 for the treatment of multiple myeloma and cholangiocarcinoma, respectively. FHND6091 not only shows great potential in the treatment of cholangiocarcinoma, but also has promising applications in the treatment of ovarian cancer, prostate cancer and other digestive malignancies. FHND6091 has opened up new avenues for the treatment of a wide range of solid tumors and is expected to bring new hope to cancer patients.

Fundamental studies

5. Anlotinib: medullary thyroid carcinoma

No.: 4665/18

Title of abstract: USP18 promotes anlotinib resistance in medullary thyroid carcinoma by stabilizing aurora B kinase

Abstract: Targeted therapy resistance is the main cause of disease progression in advanced medullary thyroid carcinoma (MTC). However, the key molecules and mechanisms remain unclear. We previously performed a genome-wide in vitro screen of anlotinib resistance-related genes in human MTC cell line TT using CRISPR-dCas9-SAM system and identified ubiquitin-specific protease 18 (USP18) as a key molecule mediating anlotinib resistance in MTC. However, its downstream mechanism needs further clarification.

Results: Based on the high-throughput DNA sequencing results of the control group and the anlotinib screening group, a group of key genes related to anlotinib resistance in MTC was screened through the MAGeCK algorithm and the enrichment ratio of sgRNA in the anlotinib screening group. Among them, USP18 ranked first in the enrichment results. Analysis of the correlation between the expression level of USP18 in MTC patient specimens and survival revealed that patients with high USP18 expression in tumor cells had poorer prognosis. Overexpression of USP18 in MTC tumor cells significantly promoted the growth of subcutaneous xenograft tumors in NOD/SCID mice treated with anlotinib. In vitro cell experiments also showed that overexpression of USP18 promoted the proliferation of MTC tumor cells and significantly inhibited the proportion of cell apoptosis after anlotinib treatment. Further research found that USP18, as a deubiquitinating enzyme that can specifically remove ISG15-like ubiquitin-like proteins from substrate proteins, can improve the kinase stability of Aurora B by removing ISG15-like ubiquitin modification and promote MTC tumor cell proliferation through the activation of PI3K-Akt signaling regulated by Aurora B kinase. Application of Aurora B kinase inhibitor in anlotinib-resistant MTC cell lines significantly inhibited tumor cell proliferation, and Aurora B kinase inhibitor significantly increased the proportion of cell apoptosis in MTC tumor cells overexpressing USP18. In the subcutaneous xenograft tumor model of MTC in NOD/SCID mice, the growth of xenograft tumors in the anlotinib combined with Aurora B kinase inhibitor treatment group was also significantly inhibited

In summary, overexpressed USP18 can activate PI3K-Akt signaling and promote tumor cell proliferation by increasing the stability of Aurora B kinase, ultimately leading to the formation of anlotinib resistance in MTC patients. Combined use of Aurora B kinase inhibitor is a potentially effective combined treatment strategy for anlotinib-resistant MTC patients.

6. Anlotinib: advanced ovarian cancer
No.: 3997/6

Title of abstract: PARP inhibitors plus anlotinib as bridging therapy for TGF β -insensitive CAR-T cell therapy targeting MSLN and CD19 in advanced ovarian cancer

Abstract: The study assessed the potential of poly (ADP-ribose) polymerase (PARP) inhibitors plus anlotinib as bridging therapy for CAR-T cells with resistance to TGF β and capability of rapid expansion by bait-and-switch strategy of dual-targeting mesothelin (MSLN) and CD19 in preclinical models of advanced ovarian cancer. Immunocompetent mice bearing ID8 tumors were treated with niraparib (21 days) plus anlotinib (14 days) and euthanized at different timepoints (0, 7, or 14 days since discontinuation) to quantify tumor-infiltrating T cells and profile T cell functions.

Results: Niraparib combined with anlotinib increased tumor-infiltrating T cells without impairing T cell functionality. The effects of promoting T cell infiltration remained significant at 14 days after discontinuation, which might associate with lasting activation of cGAS-STING pathway and secretion of downstream chemokines (CXCL10 and CCL5), and normalized tumor vasculature featured by better perfusion and reduced leakage. The engineered CAR-T cells could resist TGF β and displayed improved proliferation, cytotoxicity, cytokine release, and in vivo antitumor activities upon CD19 stimulation. Importantly, bridging therapy significantly increased CAR-T cell infiltration, curbed tumor growth, and prolonged survival in mice bearing SKOV3 CDX, HRD-negative PDX, and another multidrug-resistant PDX. PET imaging showed that bridging therapy increased tumor-infiltrating CAR-T cells and boosted tumor-killing capability.

PARP inhibitors plus anlotinib as bridging therapy facilitated CAR-T cell infiltration and enhanced antitumor activities in multiple preclinical models of advanced ovarian cancer, and an early phase I trial (NCT05141253) is ongoing to evaluate PARP inhibitors plus anlotinib as bridging therapy for CAR-T cell therapy in patients with refractory MSLN-positive ovarian cancer.

By order of the Board
Sino Biopharmaceutical Limited
Tse, Theresa Y Y
Chairwoman

Hong Kong, 10 April 2024

As at the date of this announcement, the Board of the Company comprises seven executive directors, namely Ms. Tse, Theresa Y Y, Mr. Tse Ping, Ms. Cheng Cheung Ling, Mr. Tse, Eric S Y, Mr. Tse Hsin, Mr. Tian Zhoushan and Ms. Li Mingqin and five independent non-executive directors, namely Mr. Lu Zhengfei, Mr. Li Dakui, Ms. Lu Hong, Mr. Zhang Lu Fu and Dr. Li Kwok Tung Donald.