TITLE: A single-arm phase II study of cabozantinib and atezolizumab in patients with recurrent or metastatic esophageal squamous cell carcinoma (ESCC) who failed a platinum-based chemotherapy

一項針對已接受過白金類化療之復發或轉移食道鱗狀細胞癌患者，

合併使用 **cabozantinib** 及 **atezolizumab** 的第二期臨床試驗

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PROTOCOL SYNOPSIS

STUDY TITLE*:* **A PHASE II STUDY OF CABOZANTINIB AND ATEZOLIZUMAB IN PATIENTS WITH RECURRENT OR METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC) WHO FAILED PLATINUM-BASED THERAPY**	
STUDY SCIENTIFIC OBJECTIVE	**To demonstrate that combination of cabozantinib and atezolizumab is safe and efficacious in patients with recurrent/metastatic esophageal squamous cell carcinoma (ESCC)**
STUDY DESIGN	**A single-arm, single-institute, phase II study.** The **combination of cabozantinib and atezolizumab**: • Cabozantinib 40 mg, PO, QD; • Atezolizumab 1200 mg, IV, Q3W; • Treatment will be continued until intolerable toxicities occur and/or patients no longer derive clinical benefits from the treatment. *Evaluation and follow-up:* • Clinical evaluation including blood sampling: every 3 weeks • Tumor response evaluation: every 9 weeks • Follow-up of potential treatment-related AEs will be continued until 30 days after discontinuing protocol treatment of start of next salvage treatment, whichever comes first. • The planned enrollment number of study subjects is 37. • The ORR of anti-PD-1 mAbs for R/M ESCC patients has been around 15% according to previous studies. • We hypothesize that combination of cabozantinib plus atezolizumab will improve the ORR from 15% to 30%. With one-sided, 0.1 type I error (α), 0.2 type II error (β, corresponding power: 0.8), the sample size will be 37.
STUDY POPULATION	The target population is recurrent/metastatic ESCC patients who failed first-line platinum-based chemotherapy. **<Inclusion criteria>** 1. Histologically proven squamous cell carcinoma of esophagus. 2. Progression from first-line platinum-based chemotherapy for recurrent or metastatic ESCC, or progression within 6 months after neoadjuvant, definitive, or adjuvant chemo(radio) -therapy for loco-regional ESCC. 3. Measurable disease per RECIST 1.1 4. Recovery to baseline or ≤ Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 from toxicities related to any prior treatments, unless AE(s) are clinically

nonsignificant and/or stable on supportive therapy as determined by the Investigator.

5. Age twenty years or older
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. The subject is receiving antiviral therapy per local standard of care if the subject has active HBV infection (defined by HBsAg positive); the subject must have HBV DNA < 500 IU/mL.
   - Patients with HBV infection are required to continue antiviral therapy throughout the Treatment Period, and till at least 3 months after discontinuing Trial treatment.
8. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to treatment:
   - Absolute neutrophil count (ANC) ≥ 1500/µL without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
   - White blood cell (WBC) count ≥ 2500/µL.
   - Platelets ≥ 100,000/µL without transfusion within 2 weeks before screening laboratory sample collection.
   - Hemoglobin ≥ 9 g/dL without transfusion within 2 weeks before screening laboratory sample collection.
   - Alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN).
   - Total bilirubin ≤ 1.5 mg/dL.
   - Serum albumin ≥ 2.8 g/dL.
   - Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation:
     Males: (140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)
     Females: [(140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85
   - Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h protein ≤ 1 g.
9. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document prior to any screening assessment except those procedures performed as standard of care within the screening window.
10. Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly (see Appendix G) during the course of the study and for 5 months after the last dose of study treatment. An additional contraceptive method, such as a barrier method (eg, condom), is recommended.
11. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as

premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

<Exclusion criteria>

1. Previously treated with PD-1/PD-L1 blockade or any type of small molecule kinase inhibitor (including investigational kinase inhibitor)
2. Receipt of any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) within 4 weeks before first dose of study treatment.
3. Prior radiotherapy regimen exceeding 70 Gy for a single site, including ESCC or other metastatic sites:

- For radiotherapy to treat ESCC:
  If the radiation is combined with chemotherapy, a minimum of 4 months must elapse between the end of radiotherapy and registration. If the radiation is given alone, a minimum of 8 weeks must elapse between the end of radiotherapy and registration.
- For radiotherapy to treat metastatic site:
  A minimum of 3 weeks must elapse between prior radiation and registration.
- All treatment areas should be fully healed with no sequelae from RT that would predispose to fistula formation. Unhealed or with sequelae from RT that would predispose to fistula formation.

4. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment.
5. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants:
   a. Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted.
   b. Low-dose low molecular weight heparins (LMWH) are permitted.
   c. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

6. Administration of a live, attenuated vaccine within 30 days prior to treatment.
7. Any subject who cannot be evaluated by computed tomography (CT) because of allergy or other contraindication to both CT and MRI contrast agents.
8. The subject has uncontrolled, significant intercurrent or recent (within the last 3 months before treatment [unless otherwise specified below]) illness including, but not limited to, the following conditions:

- Cardiovascular disorders:
  a. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias.
  b. Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.
  c. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event or thromboembolic event (eg, DVT, pulmonary embolism) within 6 months before treatment.
- Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
  a. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
  b. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to treatment. Complete healing of an intra-abdominal abscess must be confirmed prior to treatment.
  c. Any episodes of GI bleeding requiring transfusion or hospitalization for at least 6 months before treatment.
- Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before treatment.
- Cavitating pulmonary lesion(s) or known endobronchial invasion.
- Lesions invading major blood vessel, including, but not limited to: inferior vena cava, pulmonary artery, or aorta.
- Other clinically significant disorders such as:
  a. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see

	Appendix C for a more comprehensive list of autoimmune diseases and immune deficiencies). Subjects with the following conditions are eligible for the study: i. A history of autoimmune-related hypothyroidism and on thyroid replacement hormone ii. Controlled Type 1 diabetes mellitus and on an insulin regimen iii. Asthma that requires intermittent use of bronchodilators iv. Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only provided all of following are true: - Rash covers < 10% of body surface area - Disease is well controlled at baseline and requires only low-potency topical corticosteroids - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months b. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before treatment. Note: Inhaled, intranasal, intra-articular, and topical corticosteroids and mineralocorticoids are permitted. Transient use of systemic corticosteroids for allergic conditions such as contrast allergy is allowed. c. Active infection requiring systemic treatment, known history of infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome d. (AIDS)-related illness, or a known positive test for tuberculosis due to tuberculosis infection. Subjects with active hepatitis B virus infection controlled with antiviral therapy are eligible (see Inclusion Criterion 7). Subjects with active, uncontrolled hepatitis C virus infection are eligible provided liver function meets eligibility criteria and are receiving management of the disease per local institutional practice (note: antiviral treatment for HCV is allowed). e. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan f. Serious non-healing wound/ulcer/bone fracture. g. Malabsorption syndrome. h. Free thyroxine (FT4) outside the laboratory normal reference range. Asymptomatic subjects with FT4 abnormalities can be eligible. i. Requirement for hemodialysis or peritoneal dialysis.

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	j. History of solid organ transplant including allogeneic stem cell transplant. 9. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before treatment. Minor surgeries within 10 days before treatment. Subjects must have complete wound healing from major surgery or minor surgery before treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible. 10. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before treatment. Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility 11. History of psychiatric illness likely to interfere with ability to comply with protocol requirements or give informed consent. 12. Pregnant or breastfeeding females. 13. Inability to swallow tablets. 14. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe hypersensitivity to monoclonal antibodies. 15. Any other active malignancy at time of treatment or diagnosis of another malignancy within 2 years before treatment that requires active treatment, except for superficial skin cancer.
PRIMARY ENDPOINT	**Primary endpoints** include: • The efficacy, evaluated as objective tumor response rate (ORR) of patients with ESCC who receive the combination of cabozantinib plus atezolizumab. **Secondary endpoints** include: • Efficacy-wise: duration of response (DOR), progression-free survival (PFS), and overall survival (OS) • Safety-wise: toxicities per CTCAE 5.0 **Exploratory biomarker studies t**o search for biomarkers predictive of the efficacy of cabozantinib combined with atezolizumab and associated with outcomes of the patients will include: • Tissue-based biomarkers: PD-L1 expression by combined positive score [CPS], expression of AXL and cMET by immunohistochemistry (IHC) and gene expression profiling, immune gene expression profiles, and tumor mutational burden [TMB]); • Blood-based markers: profiling of cytokines/chemokines, and phenotyping of immune cells; • Imaging-based biomarkers: FDG-PET imaging.

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STUDY TREATMENT	**Cabozantinib 40 mg, PO, QD plus** **Atezolizumab 1200 mg, IV, Q3W;** Treatment will be continued until intolerable toxicities occur and/or patients no longer derive clinical benefits from the treatment.
FOLLOW-UP	• Clinical evaluation including blood testing: every 3 weeks • Tumor response evaluation: every 9 weeks • Follow-up of potential treatment-related AEs will be continued until 30 days after discontinuing protocol treatment of start of next salvage treatment, whichever comes first.
STATISTICAL CONSIDERATION	• The planned enrollment number of study subjects is 37. • The ORR of anti-PD-1 mAbs for R/M ESCC patients has been around 15% according to previous studies. • We hypothesize that combination of cabozantinib plus atezolizumab will improve the ORR from 15% to 30%. With one-sided, 0.1 type I error (α), 0.2 type II error (β, corresponding power: 0.8), the sample size will be 37.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Plan Summary

An overview of the endpoints and operating characteristics is shown in Table 9-1.

Table 9-1 Summary of Endpoint Operating Characteristics

Accrual per month	2 subjects
Endpoint:	**ORR (Primary endpoint)**
Power	82%
Alpha allocated (1-sided)	0.1
Assumed median, history	15%
Assumed median, experimental	30%
Estimated patient number	37
Time to enroll (months)	19
Time for follow-up (months)	6

9.2 Statistical Analysis Plan

9.2.1 Sample Size Determination

The target sample size of this prospective, single-arm, phase 2 study is 37 patients. A sample size of 37 achieves 82% power to detect a difference (P1-P0) of 0.15 using a one-sided binomial exact test. The target significance level is 0.1. These results assume that the population proportion under the null hypothesis is 0.15 and the alternative hypothesis is 0.3. The sample size was calculated by PASS. The average number of newly diagnosed ESCC patients at our center is around 180 patients per year. Among them, 30% patients present with metastatic disease and 60% patients present with locally advanced disease. Around 50% of locally advanced ESCC will have recurrent diseases indicated for this study. We plan to enroll 2 patients per month into this trial. Therefore, the estimated duration of total enrollment will be 19 months. With additional follow-up of 6 months after the last enrollment, the whole study period of the trial will be 25 months.

The primary objective of the study is to improve overall response rate for recurrent or metastatic ESCC patients who have failed a platinum-based chemotherapy. The secondary objectives of the study included the median progression-free survival, overall survival, and safety and toxicity. According to the two phase III global clinical trials (KEYNOTE-181 and ATTRACTION-3), the ORR for second-line immune checkpoint inhibitors is around 15%. We estimated the ORR could improve to 30% in the combination of atezolizumab and cabozantinib.

9.2.2 Definition of Variables

Overall response rate (ORR) is the proportion of patients whose tumor is significantly reduced. ORR is generally defined as the sum of complete responses (CRs) – patients with no detectable evidence of a tumor over a specified time period – and partial responses (PRs) – patients with a decrease in tumor size over a specified time period. The response will be recorded after each response evaluation by an imaging study (CT scan), and the updated best of response will be adopted for final analysis of the primary endpoint. Progression-free survival (PFS) is the time from enrollment to the first occurrence of disease progression or death from any cause (whichever occurs first) and will be conducted in the whole study population. It is designed to include progression events as determined by the investigators per RECIST 1.1 or death. Patients who have neither progressed nor died or who are lost to follow-up are censored at the date of the last tumor assessment or last follow up for progression of disease. Patients for whom no post-baseline tumor assessments are available are censored at day 1.

Overall survival (OS) is the time from enrollment to death of any cause or the last follow-up (censored).

Evaluation of Toxicity: The incidence and severity of toxicity will be summarized according to the NCI Common Toxicity Criteria Version 4.0.

9.2.3 General Statistical Consideration

Statistical analysis for ORR and safety will be performed for subjects given at least one dose of the investigational product. Statistical analyses for PFS, OS will be performed for intention-to-treat population.

Our hypothesis is that combinational treatment with ORR as 30% is superior to historical ORR of a single agent atezolizumab as 15%. To control type I error under one-sided 10%, with power of 80%, we'll use the exact method of one-sample inference for a binomial proportion. For the percentages of CR, PR and SD, the corresponding 95% CI will be estimated using the Clopper-Pearson method for each treatment group.

Final analysis will be done when the last patient enrolled has been treated for 6 months.

The survival estimates will be derived from Kaplan and Meier curves.