ELIGIBILITY CRITERIA FOR PROVIDERS

A Randomized Phase 2b/Phase 3 Study of the TGF-β2 Targeting Antisense Oligonucleotide OT-101 in Combination with mFOLFIRINOX Compared with mFOLFIRINOX Alone in Patients with Advanced and Unresectable or Metastatic Pancreatic Cancer.

MENU

STUDY OBJECTIVES

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Part 1: Lead-in for Safety, Tolerability and PK

Primary Objective

- To determine the maximum tolerated dose (MTD) of OT-101 in patients with advanced and unresectable or metastatic pancreatic cancer when it is combined with mFOLFIRINOX.

Secondary Objective

- To characterize the PK of OT-101 when it is combined with mFOLFIRINOX in patients with advanced and unresectable or metastatic pancreatic cancer.

Part 2: Randomized portion of the study

Primary Objective

- To compare the efficacy of OT-101 in combination with mFOLFIRINOX versus mFOLFIRINOX alone in patients with advanced and unresectable or metastatic pancreatic cancer as measured by overall survival (OS)

Secondary Objective

- To assess the efficacy of OT-101 in combination with mFOLFIRINOX in patients with advanced and unresectable or metastatic pancreatic cancer as measured by:
  - Progression-free survival (PFS)
  - Objective response rate (ORR), by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1
- To compare the safety and tolerability of OT-101 in combination with mFOLFIRINOX versus mFOLFIRINOX alone

Exploratory Objectives

- To further explore treatment efficacy in tumor response as measured by:
  - Disease control rate (DCR)
  - Duration of response (DoR)
  - 1-year survival rate
- To explore biomarkers that may correlate with tumor response, immune activation, and relationships to clinical efficacy outcomes.
- To explore associations between patient-reported symptoms, functioning, and global health status/QoL using the European Organization for Research and Treatment of Cancer Quality of Life Core 30-item (EORTC QLQ-C30) questionnaire as well as current health status and the EuroQoL 5-dimension (EQ-5D) Index used in the economic evaluation of health care using the EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire.

STUDY ENDPOINTS

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Part 1: Lead-in for Safety, Tolerability and PK

Primary Endpoint

- Incidence of dose limiting toxicities (DLTs)

Secondary Endpoints

- PK Parameters

Safety Endpoints

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Abnormal laboratory parameters
- Abnormal vital signs
- Physical examination findings
- ECG findings

Part 2: Randomized portion of the study

Primary Endpoint:

The primary endpoint is OS, defined as the time from date of Randomization to death due to any cause

Secondary Endpoint:

- PFS defined as the time from date of Randomization to the earlier of first documentation of definitive disease progression (the initial PD that was confirmed by the consecutive scan) or death due to any cause.
- ORR defined as the proportion of patients who achieve a CR or PR as assessed by RECIST v.1.1.

Exploratory Endpoints:

- DCR defined as proportion of patients who achieve a SD, PR or CR as assessed by RECIST v1.1.
- DoR defined as the time from the date of the first documentation of objective tumor response (CR or PR) to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurs first.
- 1-year OS rate is defined as the survival rate as estimated using the Kaplan-Meier method at the end of the first year.
- Baseline and change from baseline in immune and molecular biomarkers and their relationship to clinical efficacy endpoints will be explored. In addition to baseline and change from baseline in the EORTC QLQ-C30 and EQ-5D-5L, time to deterioration in patient-reported symptoms and functioning will be explored using symptom items that correspond with the TEAE profile (eg, fatigue, anorexia, and nausea/vomiting) as well as the subscales for functioning and HRQoL.

Safety Endpoints:

- Incidence of dose limiting toxicities (DLTs)
- Adverse events (AEs)
- Serious adverse events (SAEs)
- Abnormal laboratory parameters
- Abnormal vital signs
- Physical examination

INCLUSION CRITERIA

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1. A diagnosis of advanced and unresectable or metastatic pancreatic adenocarcinoma confirmed by:
   a. Histopathology from primary tumor in pancreas, OR
   b. Histopathology from a non-pancreatic lesion in the presence of a mass in the pancreas consistent with pancreatic adenocarcinoma or a medically documented history of pancreatic adenocarcinoma.
2. Measurable disease per RECIST v.1.1
3. Male or non-pregnant, non-lactating female, ≥18 years or age
   a. If a female patient is of child-bearing potential, as evidenced by menstrual periods, shemust have a negative serum pregnancy test (beta-human chorionic gonadotropin [β- hCG]) documented prior to the first administration of study drugs.
   b. Female patients of childbearing age and women < 12 months since the onset of menopause must agree to use acceptable contraceptive methods for the duration of the study and 9 months following the last injection of OT-101. If employing contraception, two of the following precautions must be used: birth control pill, vasectomy of partner, tubal ligation, vaginal diaphragm, intrauterine system (IUS) or intrauterine device (IUD), condom and vaginal spermicide, or total abstinence. Male patients must be surgically sterile or must agree to use a condom and acceptable contraceptive method with their female partners. Female patients who are post-menopausal are defined as those with an absence of menses for > 12 consecutive months. In addition, male and female patients must utilize contraception after the end of the treatment as recommended in the individual drugs comprising mFOLFIRINOX product's Summary of Product Characteristics or Prescribing Information
   c. Male patients must use effective contraception for a duration of 6 months after the final dose, as per the prescribing information for oxaliplatin.
4. Provide signed written informed consent
5. Eastern Cooperative Group (ECOG) Performance Status (PS) score of 0–1
6. Willingness and ability to comply with study requirements
7. Patient has adequate organ function by the following laboratory assessments at baseline(obtained ≤28 days prior to Randomization):
   a. Hematologic
      - Platelets $\geq 100 \times 10^9$/L
      - Hemoglobin ≥9.0 g/dL
      - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9$/L
      - Patient has acceptable coagulation values obtained ≤28 days prior to Randomization as demonstrated by prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT) ≤1.5× upper limit of normal (ULN) (if on Coumadin, patient must be changed to LMWH or on Factor II or Xa anticoagulant with a t½ of less than 24 hours

b. Hepatic

- Aspartate transaminase (AST)/alanine transaminase (ALT) ≤3×ULN (if liver metastases are present, ≤5×ULN)
- Alkaline phosphatase ≤2.0×ULN (if liver metastases are present, ≤5×ULN)
- Total bilirubin ≤2.0×ULN (in patients with Gilbert's Syndrome total bilirubin < or = 2.5xULN)

c. Renal

- Calculated creatinine clearance ≥50 mL/min. Actual body weight should be used for calculating creatinine clearance (e.g., using the Modification of Diet in Renal Disease [MDRD] formula. For patients with a body mass index (BMI) >30 kg/m^2, lean body weight should be used instead

8. Patient must have a life expectancy of ≥3 months in the opinion of the Investigator

EXCLUSION CRITERIA

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1. Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie lymphoma, sarcoma), adenocarcinoma originating from the biliary tree, or cystadenocarcinoma
2. Patient has experienced a decrease in ECOG PS (Appendix 4) between Screening visit and within 72 hours prior to Randomization
3. Patient on Coumadin and not willing to change to LMWH or oral Factor II or Xa inhibitor with t½ of less than 24 hours
4. History of prior malignancy, except for adequately treated in situ cancer, basal cell, squamous cell skin cancer, or other cancers (eg, breast and prostate) for which the patient has been disease-free for at least 3 years. Patients with prior cancer that is adequately controlled per the judgement of the Investigator will not be excluded from the study
5. Any serious medical condition, laboratory abnormality, psychiatric illness, or comorbidity that, in the judgment of the Investigator, would make the patient inappropriate for the study
6. Patients with abnormal electrocardiogram (ECG) at baseline (QT or QTc interval >470 ms) will be excluded from this study. The eligibility of patients with ventricular pacemakers for whom the QT interval may not be accurately measurable will be determined on a case-by-case basis by the Sponsor's medical representative in consultation with the principal investigator.
7. Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires intravenous antibiotics
8. Known history of positivity (regardless of immune status) for human immunodeficiency virus (HIV)
9. Known history of chronic active or active viral hepatitis A, B, or C infection
10. Clinically significant bleeding within 2 weeks prior to Randomization (eg, gastrointestinal[GI] bleeding or intracranial hemorrhage)
11. Pregnant or lactating women
12. Myocardial infarction, coronary bypass surgery, or arterial thromboembolic events within the last 6 months prior to Randomization, symptomatic congestive heart failure (New York Heart Association Classification >Class II, unstable angina, or unstable cardiac arrhythmia requiring medication
13. Clinically significant ascites defined as requiring ≥1 paracentesis every 2 weeks
14. Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days prior to Randomization or anticipated surgery during the study period
15. Prior history of receiving immune checkpoint inhibitors (anti-CTLA4, anti-PD1, anti-PD-L1)
16. Peripheral neuropathy (>Grade 1)
17. Known history of dihydropyrimidine dehydrogenase deficiency (DPD) — Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in the catabolism of 5-fluorouracil (5-FU). Thus, patients with a DPD deficiency are at risk of developing severe 5-FU-associated toxicity

18. History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegner´s granulomatosis, Sjogren´s syndrome, Bell´s palsy, Guillain-Barre syndrome, multiple sclerosis, vasculitis, or glomerulonephritis, except for psoriasis not requiring systemic therapy, vitiligo or alopecia areata, or hypothyroidism
19. Patients receiving any of the following medications are not eligible for study:
    a. Investigational agents other than the protocol drugs
    b. Anti-coagulants (except for heparin to maintain the patency of central venous catheters)
    c. Non-steroidal anti-inflammatory drugs
    d. Clopidogrel (Plavix), dipyridamole (Persantine), or any other drug that inhibits platelet functions.
    e. Patients on greater than 2 mg dexamethasone, 10 mg Prednisone or equivalent dose in alternate corticosteroid daily or actively undergoing corticosteroid dose escalation are NOT eligible.
20. History of allergic reactions or known hypersensitivity to compounds of similar chemical or biologic composition to OT-101 such as anti-sense oligonucleotides or siRNA
21. Patients who are unable to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy. Telemedicine visits are acceptable.
22. Not willing and able to comply with study requirements including protocol mandated procedures and visits
23. Other contraindications as defined in the product label of the components of the mFOLFIRINOX treatment regimen
24. Participation in another investigational clinical trial within 30 days of receiving the last dose of investigational study drug
25. Clinically significant psychiatric disorders, legal incapacity or limited legal capacity
26. Patients with a primary immunodeficiency
27. Patients with active central nervous system (CNS) metastases. (Patients with adequately treated CNS metastases who are clinically stable for at least 6 weeks after discontinuation of corticosteroids may be eligible for enrollment with the approval of the Sponsor’s medical representative and the principal investigator)