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

Back to menu

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

Back to menu

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

Back to menu

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
   b. 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 anticoagulation is medically required the patient must be on

an agent which is promptly reversible with readily available drugs as detailed in Exclusion Criteria #3)

c. 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)

d. 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

Back to menu

1. Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie lymphoma, sarcoma), adenocarcinoma originating from the biliary tree, or cystadenocarcinom
2. Patient has experienced a decrease in ECOG PS (Appendix 4) between Screening visit and within 72 hours prior to Randomization
3. Bleeding diathesis due to underlying medical condition or anticoagulation which is unable to be promptly reversed by medical treatment.

   The chronic use of the following anticoagulants is allowed:

   - Vitamin K antagonists (warfarin, acenocoumarol)
   - Heparin and low molecular weight heparin
   - Direct acting anti-Factor Xa oral anticoagulants (DOACs) – (apixaban, rivaroxaban)
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. Anticoagulants including anti-platelet agents the effect of which are unable to be promptly reversed by medical treatment
    c. Non-steroidal anti-inflammatory drugs
    d. Patients on chronic, daily corticosteroids receiving a dose of ≥ 10 mg prednisone p.o. daily. Short courses lasting two weeks or less of high dose systemic corticosteroids for treatment of such medical conditions as acute asthma, acute exacerbations of COPD, relief of symptoms associated with palliative RT, prophylaxis against allergic reactions to contrast agents for imaging studies, etc. may be administered with the joint approval of the investigator and the sponsor's medical representative.
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)

SCIENTIFIC UPDATE

Back to menu

The current study OT-01-P201 (STOP-PC) is a follow-on phase 2/3 trial building on five previous clinical trials conducted in Korea, the US, and the EU. These include two phase 2 trials involving over 200 patients:

- **P001:** A phase 2 trial assessing the safety and tolerability of OT-101 administered intravenously in patients with advanced tumors overproducing TGF-β2 (ClinicalTrials.gov ID: NCT00844064).
- **G004:** A phase 2b trial evaluating the TGF-β2 antisense compound OT-101 in recurrent or refractory high-grade glioma (ClinicalTrials.gov ID: NCT00431561).

In these studies, **OT-101** demonstrated clinical benefits in pancreatic ductal adenocarcinoma (PDAC), melanoma, and glioma, including documented cases of complete remission.

OT-101 works by adopting the patient's immune system to target and eradicate tumors through the suppression of **TGF-β2**, a cytokine implicated in immune evasion and tumor progression.

Median survival for patients with low TGF-β2 expression was **72 months**, compared to **15 months** for those with high TGF-β2 levels.

When combined with irinotecan (a core component of the mFOLFIRINOX regimen), **OT-101** extended median survival to over **34 months** in patients with low **TGF-β2** expression. Importantly, the modified FOLFIRINOX regimen (mFOLFIRINOX) used in STOP-PC has been shown to be **safer** while maintaining efficacy comparable to traditional FOLFIRINOX.

Recent developments further support OT-101's potential:

- A **phase 1b trial** combining **OT-101** with IL-2 in solid tumors identified an **optimal dose of 140 mg/m².**
- New research highlights the critical role of **TGF-β2** in the progression of various tumor types, including PDAC, suggesting OT-101 could significantly benefit these patients.

2024 peer reviewed publications are available at Pubmed as follow:

1. TGFB2 mRNA Levels Prognostically Interact with Interferon-Alpha Receptor Activation of IRF9 and IFI27, and an Immune Checkpoint LGALS9 to Impact Overall Survival in Pancreatic Ductal Adenocarcinoma. Qazi S, Trieu V. Int J Mol Sci. 2024 Oct 18;25(20):11221. doi: 10.3390/ijms252011221. PMID: 39457004 (https://pubmed.ncbi.nlm.nih.gov/39457004/)
2. Transforming Growth Factor Beta 2 (TGFB2) mRNA Levels, in Conjunction with Interferon-Gamma Receptor Activation of Interferon Regulatory Factor 5 (IRF5) and Expression of CD276/B7-H3, Are Therapeutically Targetable Negative Prognostic Markers in Low-Grade Gliomas. Trieu V, Maida AE, Qazi S. Cancers (Basel). 2024 Mar 19;16(6):1202. doi: 10.3390/cancers16061202. PMID: 38539537 Free PMC article. (https://pubmed.ncbi.nlm.nih.gov/38539537/)
3. Transforming Growth Factor Beta 2 (TGFB2) and Interferon Gamma Receptor 2 (IFNGR2) mRNA Levels in the Brainstem Tumor Microenvironment (TME) Significantly Impact Overall Survival in Pediatric DMG Patients. Qazi S, Talebi Z, Trieu V.

Biomedicines. 2024 Jan 15;12(1):191. doi: 10.3390/biomedicines12010191. PMID: 38255296 Free PMC article. (https://pubmed.ncbi.nlm.nih.gov/38255296/)

4. High Intra-Tumor Transforming Growth Factor Beta 2 Level as a Predictor of Poor Treatment Outcomes in Pediatric Diffuse Intrinsic Pontine Glioma. Uckun FM, Qazi S, Trieu V. Cancers (Basel). 2023 Mar 9;15(6):1676. doi: 10.3390/cancers15061676. PMID: 36980562 Free PMC article. (https://pubmed.ncbi.nlm.nih.gov/36980562/)