TRIDENT: A Phase 2 Study of Relacorilant Plus Nab-paclitaxel and Gemcitabine in Chemotherapy-naïve Patients With Metastatic Pancreatic Ductal Adenocarcinoma

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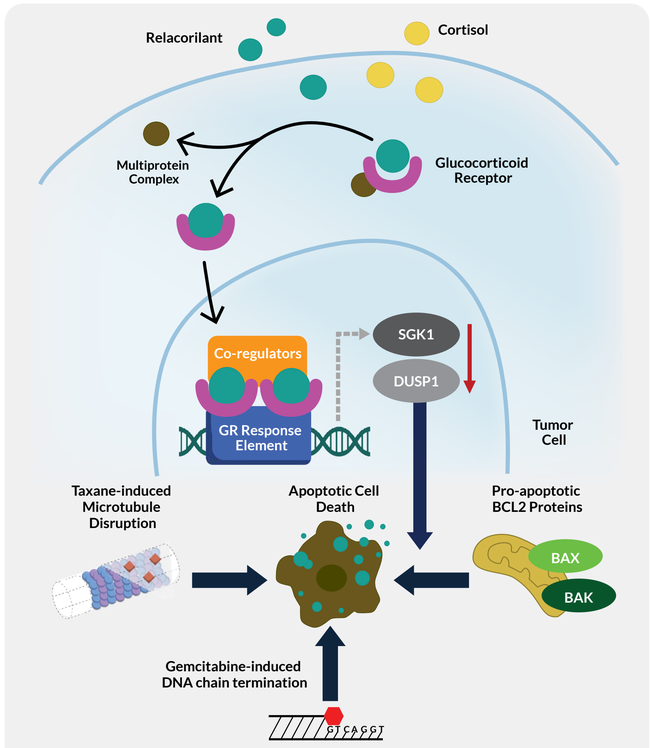
SUMMARY AND CONCLUSIONS

- Patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) have limited treatment options and a poor prognosis
- Relacorilant is a selective glucocorticoid receptor antagonist (SGRA) that increases the sensitivity of tumors that express the glucocorticoid receptor (GR) to cytotoxic chemotherapies
  - Many solid tumors, including pancreatic and ovarian cancers, express high levels of the GR
  - In the phase 3 ROSELLA study, relacorilant in combination with nab-paclitaxel demonstrated significantly improved progression-free and overall survival in patients with platinum-resistant ovarian cancer (PROC), with a manageable safety profile
  - Relacorilant was recently approved in the United States, in combination with nab-paclitaxel, for the treatment of adult patients with PROC who have received 1–3 prior lines of therapy, at least one of which included bevacizumab
- The phase 2 TRIDENT study is assessing treatment with relacorilant + nab-paclitaxel + gemcitabine in patients with chemotherapy-naïve mPDAC

BACKGROUND AND MECHANISM OF ACTION

- Pancreatic cancer is the third leading cause of cancer death in the United States and is expected to become the second leading cause of cancer-related mortality by 2030[1,2]
- Pancreatic ductal adenocarcinoma (PDAC) accounts for ~90% of pancreatic cancers, and up to 80% of patients with PDAC are diagnosed at an advanced stage[3]
- Patients with metastatic PDAC (mPDAC) have a poor prognosis, with a 5-year survival rate of 3%[4,5]
  - Standard first-line treatment options for patients with mPDAC are modified fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX); fluorouracil, leucovorin, liposomal irinotecan, and oxaliplatin (NALIRIFOX); and nab-paclitaxel + gemcitabine[6-8]
  - In clinical trials, the median progression-free survival (PFS) of these regimens in the first-line setting ranges from 4 to 7 months, and the median overall survival (OS) ranges from 7 to 17 months[5-10]
- Many solid tumors, including pancreatic and ovarian cancers, express high levels of the glucocorticoid receptor (GR)[11]
  - Cortisol-mediated GR activation provides prosurvival signals to tumor cells that contribute to chemotherapy resistance[12-17]
  - High GR expression in PDAC is associated with shorter OS[18]
- Relacorilant is an orally administered, reversible, selective GR antagonist (SGRA) that has been shown to increase the sensitivity of GR-expressing tumors to cytotoxic chemotherapy and may indirectly activate the immune system (**Figure 1**)[19,20]
  - Relacorilant was recently approved in the United States, in combination with nab-paclitaxel, for the treatment of adult patients with platinum-resistant ovarian cancer (PROC) who have received 1–3 prior lines of therapy, at least one of which included bevacizumab [21]
  - In the phase 3 ROSELLA study, relacorilant demonstrated significantly improved PFS and OS in patients with PROC and had a manageable safety profile[22,23]
- The addition of relacorilant to paclitaxel + gemcitabine improved tumor growth inhibition over paclitaxel + gemcitabine alone in a PDAC xenograft model[24]
- Additionally, 2 patients with PDAC showed durable, confirmed partial responses to relacorilant + nab-paclitaxel in a phase 1 study[25]

Figure 1. Relacorilant MOA



Pro-apoptotic Synergy With Taxanes and Gemcitabine

BCL2, B-cell lymphoma 2; BAK, BCL2 homologous antagonist/killer; BAX, BCL2-associated X protein; DUSP1, dual specificity phosphatase 1; GR, glucocorticoid receptor; MOA, mechanism of action; SGK1 serum/glucocorticoid-regulated kinase 1.

METHODS

Study Design

- TRIDENT (NCT07259317) is a 2-part (dose-finding and expansion), phase 2, open-label, multicenter study in patients with mPDAC (**Figure 2**)

Dose-finding Part 1 Endpoints

- **Primary:**
  - Safety and tolerability, evaluated via dose-limiting toxicities (DLTs); adverse events (AEs); serious AEs (SAEs); and dose modifications and treatment discontinuations due to AEs
  - MTD and/or the optimal dose/schedule of relacorilant, gemcitabine, and nab-paclitaxel when given in combination, with MTD defined as the most intense dose/schedule among those evaluated at which <33% of patients experience a DLT
- **Secondary:**
  - Pharmacokinetics (PK) of relacorilant and nab-paclitaxel

Expansion Part 2 Endpoints

- **Primary:**
  - Investigator-assessed PFS
- **Secondary:**
  - OS, best overall response, overall response rate, duration of response, clinical benefit rate at 24 weeks, and reductions in cancer antigen 19-9
  - Safety of relacorilant in combination with gemcitabine and nab-paclitaxel
  - PK of relacorilant and nab-paclitaxel

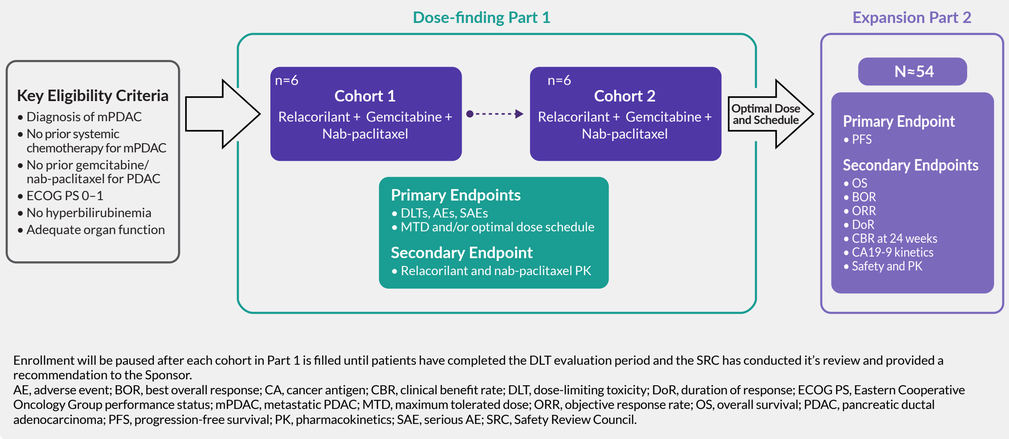
Statistical Considerations

- Efficacy will be analyzed in the efficacy population (patients who receive ≥1 dose at the optimal dose and schedule). Safety will be analyzed in the safety population (patients who receive ≥1 dose of study treatment) and the efficacy population
- Time-to-event endpoints will be estimated using Kaplan-Meier methods, with 95% confidence intervals (CIs) calculated using the Brookmeyer and Crowley method. Other secondary endpoints will be characterized by descriptive or summary statistics

Study Sites

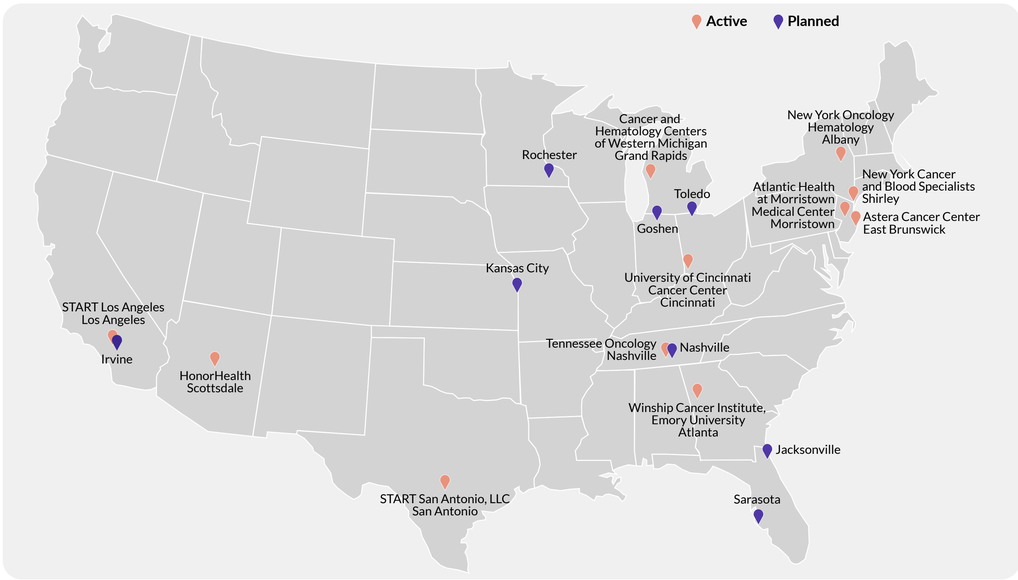
- The study is being conducted at up to 30 sites in the United States (**Figure 3**), and enrollment is currently ongoing

Figure 2. TRIDENT Study Schema



Enrollment will be paused after each cohort in Part 1 is filled until patients have completed the DLT evaluation period and the SRC has conducted it's review and provided a recommendation to the Sponsor.
AE, adverse event; BOR, best overall response; CA, cancer antigen; CBR, clinical benefit rate; DLT, dose-limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mPDAC, metastatic PDAC; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PK, pharmacokinetics; SAE, serious AE; SRC, Safety Review Council.

Figure 3. TRIDENT Study Sites



Eligibility Criteria

Key Inclusion Criteria
Adults aged ≥18 years with a histologic or cytologic diagnosis of PDAC
Initial metastatic disease diagnosis ≤9 weeks prior to enrollment
Life expectancy ≥3 months
≥1 measurable distant tumor metastasis per RECIST v1.1
ECOG performance status 0 or 1
Able to swallow and retain oral medication and does not have uncontrolled emesis
Adequate gastrointestinal absorption[a]
Adequate hematologic, renal, hepatic, and coagulation function[b]
Received no prior systemic anticancer chemotherapy to treat mPDAC; treatment with single agent RAS inhibitor is permitted if the last dose of RAS inhibitor was taken ≤8 weeks prior to C1D1
If a patient received prior PDAC treatment with chemotherapy in the adjuvant setting, disease progression must have occurred >12 months after the last dose, and there are no persistent treatment-related toxicities
Negative pregnancy test for patients of childbearing potential

Key Exclusion Criteria
Major surgery within 4 weeks
Prior treatment with: ▪ Radiotherapy, surgery, chemotherapy, investigational therapy for the treatment of metastatic disease ▪ Systemic, inhaled, or prescription strength topical corticosteroids within ≤5 half-life periods ▪ Gemcitabine or nab-paclitaxel
Known germline or somatic BRCA mutation
Peripheral neuropathy grade >1
Requirement for chronic or frequent corticosteroids
History of severe hypersensitivity or severe reaction to any study drug or their excipients
Concurrent use of mifepristone or other GR modulators
Clinically significant uncontrolled conditions[c]
Active infection with HIV, hepatitis C, or hepatitis B virus
Untreated parenchymal brain metastasis or uncontrolled CNS metastases
History of other malignancy within 3 years prior to enrollment

[a]Adequate absorption required in patients with prior gastric/gastrointestinal/hepatobiliary surgery; ≥7 days of enzyme replacement therapy for patients with pancreatic insufficiency. [b]Defined as ANC ≥1,500 cells/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9 g/dL, bilirubin ≤1.5×ULN, ALT or AST ≤2.5×ULN, albumin ≥3.0 g/dL, eCrCl ≥35 mL/min, PT or international normalized ratio within 1.5×ULN and PTT within 1.5×ULN. No G-CSF or transfusion for hematologic support allowed 2 weeks prior to screening labs. [c]Includes but not limited to pancreatitis, unstable angina or myocardial infarction ≤6 months of C1D1, congestive heart failure NYHA class ≥II, grade ≥3 arrhythmias, cirrhosis, gastric-outlet obstruction, acute renal failure, and uncontrolled hypertension.
ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BRCA, breast cancer gene; C, cycle; CNS, central nervous system; D, day; ECOG, Eastern Cooperative Oncology Group; eCrCl, estimated creatinine clearance; G-CSF, granulocyte-colony–stimulating factor; GR, glucocorticoid receptor; mPDAC, metastatic PDAC; NYHA, New York Heart Association; PDAC, pancreatic adenocarcinoma; PT, prothrombin time; PTT, partial thromboplastin time; RAS, rat sarcoma; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

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