Safety and Tolerance of Epigenetic and Immunomodulating Drugs Combined With Chemotherapeutics in Patients Suffering From Advanced Pancreatic Cancer

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT04257448	RECRUITING	FEBRUARY 6, 2020	MAY 5, 2021

STUDY DESCRIPTION

Brief Summary

A multi-center, open-label phase I/II study to to determine the safety and tolerability of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine in patients with advanced pancreatic ductal adenocarcinoma (PDAC) (Part 1), followed by sequential immune targeting with programmed death-ligand (PD-L)1 blockade in combination with low-dose Lenalidomide (Part 2) in patients with controlled disease after 3 cycles (Part 1).

Condition or Disease: Pancreas Cancer
Pancreatic Adenocarcinoma
Pancreatic Ductal Adenocarcinoma

Intervention/treatment: Drug: Romidepsin
Drug: Azacitidine
Drug: nab-Paclitaxel
Drug: Gemcitabine
Drug: Durvalumab
Drug: Lenalidomide capsule

Phase: Phase 1/Phase 2

DETAILED DESCRIPTION

The first part of the study will employ a standard 3 + 3 design to test safety and tolerability of histone deacetylase (HDAC) inhibition with Romidepsin (Arm A), DNA methyltransferase (DNMT) inhibition with Azacitidine (Arm B) or both agents (Arm C), in each arm in combination with nab-Paclitaxel/Gemcitabine (Part 1a). Study treatment is given until intolerable toxicity as defined in the protocol. Treatment will escalate until the recommended dose for RDE is identified.
For the expansion part (Part 1b) of the study, one of the treatment arms (Arm C over B over A) will be continued using a Simon Two-stage design to a maximum of 35 patients.
All patients from Part 1a and 1b will be treated for a total of three cycles and will then enter the second part of the study in case of disease control with still measurable disease (PR, SD).
In the second part (Part 2) of the study (consolidation therapy), all patients from Part 1 (dose escalation and expansion cohorts from experimental arms and standard arm) who have not progressed after three cycles of nab-Paclitaxel/Gemcitabine with or without additional epigenetic treatment (= at least SD by RECIST 1.1 after 3 cycles) receive sequential immune targeting with PD-L1 blockade (standard fixed dose Durvalumab 1500 mg q4w iv) in combination with low-dose Lenalidomide (10 mg d1-21 q4w po) until documented disease progression.

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 75 participants

Intervention Model : Sequential Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Multicenter, Phase I/II Study of Sequential Epigenetic and Immune Targeting in Combination With Nab-Paclitaxel/Gemcitabine in Patients With Advanced Pancreatic Ductal Adenocarcinoma.

Actual Study Start Date: May 2020

Estimated Primary Completion Date: March 2024

Estimated Study Completion Date: March 2024

ARMS AND INTERVENTIONS

Arm	Intervention/treatment

Experimental: Arm C or B or A In Part 1b (expansion part) of the study, one of the treatment arms (Arm C over Arm B over Arm A) will be continued. Treatment will only be performed with the study drug that were tolerable in Part 1a (dose escalation).	Drug: Romidepsin Powder and solvent for solution for infusion; Intravenous use Drug: Azacitidine Powder for suspension for injection; Subcutaneous use Drug: nab-Paclitaxel Powder for suspension for injection; Intravenous use Drug: Gemcitabine Powder for solution for infusion; Intravenous use
Experimental: Romidepin/Azacitidine/nab-Paclitaxel/Gemcitabine (Arm C) Part 1a: The intervention to be administered depends on the determined dose in Arm A and Arm B. Additionally nab-Paclitaxel (125 mg/m²)/Gemcitabine (1000 mg/m²) will be given on Day 1, Day 8 and Day 15 (every 28 days) of each treatment cycle. Study treatment is given until intolerable toxicity or will escalate until the recommended dose for expansion for a maximum of 3 cycles.	Drug: Romidepsin Powder and solvent for solution for infusion; Intravenous use Drug: Azacitidine Powder for suspension for injection; Subcutaneous use Drug: nab-Paclitaxel Powder for suspension for injection; Intravenous use Drug: Gemcitabine Powder for solution for infusion; Intravenous use
Experimental: Romidepsin/nab-Paclitaxel/Gemcitabine (Arm A) Part 1a: Romidepsin (2 mg/m² or 3.3 mg/m² or 7 mg/m²) will be administered in combination with nab-Paclitaxel (125 mg/m²)/Gemcitabine (1000 mg/m²) on Day 1, Day 8 and Day 15 (every 28 days) of each treatment cycle. Study treatment is given until intolerable toxicity or will escalate until the recommended dose for expansion for a maximum of 3 cycles.	Drug: Romidepsin Powder and solvent for solution for infusion; Intravenous use Drug: nab-Paclitaxel Powder for suspension for injection; Intravenous use Drug: Gemcitabine Powder for solution for infusion; Intravenous use
Experimental: Azacitidine/nab-Paclitaxel/Gemcitabine (Arm B) Part 1a: Azacitidine (20 mg/m² or 30 mg/m² or 40 mg/m²) will be administered on Days -7 to Day -3 of each treatment cycle. Additionally nab-Paclitaxel (125 mg/m²)/Gemcitabine (1000 mg/m²) will be given on Day 1, Day 8 and Day 15 (every 28 days) of each treatment cycle. Study treatment is given until intolerable toxicity or will escalate until the recommended dose for expansion for a maximum of 3 cycles.	Drug: Azacitidine Powder for suspension for injection; Subcutaneous use Drug: nab-Paclitaxel Powder for suspension for injection; Intravenous use Drug: Gemcitabine Powder for solution for infusion; Intravenous use
Active Comparator: nab-Paclitaxel/Gemcitabine (Standard Arm) nab-Paclitaxel (125 mg/m²)/Gemcitabine (1000 mg/m²) will be administered on Day 1, Day 8 and Day 15 (every 28 days) of each treatment cycle.	Drug: nab-Paclitaxel Powder for suspension for injection; Intravenous use Drug: Gemcitabine Powder for solution for infusion; Intravenous use
Experimental: Durvalumab/Lenalidomide Part 2: All patients from Part 1 who have not progressed after three cycles receive standard fixed dose Durvalumab (1500 mg) on Day 1 of each 28-day treatment cycle by IV infusion in combination with orally administered low-dose Lenalidomide (10 mg) on Days 1 to 21 until documented disease progression. Study treatment is given for a maximum of 13 cycles.	Drug: Durvalumab Concentrate for solution for infusion; Intravenous use Drug: Lenalidomide capsule Hard capsule for oral use

OUTCOME MEASURES

Primary Outcome Measures:
1. Safety and tolerability of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine [Time Frame: at Days -7, -4, 1, 8, 15, 22 at cycle 1 (each cycle is 28 days)]
Dose limiting toxicities occurring during treatment cycle 1 of a respective dose level and regarded to be related to the studied drug combination. Common terminology criteria for adverse events (CTCAE) 5.0 will be used to assess toxicities.
2. Immune targeting with Durvalumab in combination with low-dose Lenalidomide [Time Frame: up to 13 cycles (each cycle is 28 days)]
The efficacy and safety of this experimental (immune) consolidation therapy during this clinical trial will be monitored by imaging changes every 8 weeks.
3. Immune targeting with Durvalumab in combination with low-dose Lenalidomide [Time Frame: up to 13 cycles (each cycle is 28 days)]
The efficacy and safety of this experimental (immune) consolidation therapy during this clinical trial will be monitored closely by tumor marker changes on Day 1 of each cycle.
4. Recommended dose for expansion (RDE) [Time Frame: at the end of cycle 3 (each cycle is 28 days)]
Identification of the recommended dose for expansion of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine.

Secondary Outcome Measures:
1. Overall response rate (ORR) [Time Frame: up to 16 months]
Part 1: ORR according to RECIST version 1.1 (complete response [CR] and partial response [PR]) after respective treatment) every 6 weeks Part 2: ORR according to immune related RECIST 1.1 (irRECIST1.1) (CR and PR) after/during treatment with Lenalidomide and Durvalumab every 8 weeks
2. Carbohydrate Antigen 19-9 (CA19-9) Response [Time Frame: at Day 1 of each treatment cycle (each cycle is 28 days), up to 16 month]
Part 1: CA19-9 Response: CA19 -9 change after treatment compared to baseline level Part 2: 2nd CA19-9 Response: CA19 -9 change after treatment compared to last level determined in Part 1
3. Disease-control rate (DCR) [Time Frame: at the end of cycle 3 and 6 (each cycle is 28 days)]
Part 1: DCR at 3-month according to RECIST version 1.1 (CR and PR and stable disease [SD] after respective treatment Part 2: 2nd DCR at 3-month and 6-month according to irRECIST1.1 (CR and PR and stable disease [SD] after respective treatment)
4. Overall survival (OS) [Time Frame: at Day 1 of cycle 1 (each cycle is 28 days) until death or up to 4 years]
Time from Day 1 of the first cycle of chemotherapy to date of death from any cause. The rate of patients who are still alive after one year will be assessed.
5. Progression free survival (PFS) [Time Frame: D1 of the first cycle (each cycle is 28 days), up to 16 month]
Time from Day 1 of the first cycle of chemotherapy to date of objective disease progression or to death of any cause.

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
- Patients must have histologically confirmed PDAC
- Patients must have metastatic disease (stage IV) and not received prior chemotherapy for stage IV disease
- Patients must not have received the following drugs before: Azacitidine, Romidepsin, any checkpoint-inhibitor or immunomodulating agents such as Immunomodulatory imide drugs (IMiDs)
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v. 1.1
- Male or female, age ≥ 18 years
- Body weight > 30 kg for inclusion into Part 2
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Patients must have normal organ and marrow function
- Patients must be recovered from the effects of any prior surgery
- Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up
- All subjects must agree to refrain from donating blood while on study drug and for 90 days after discontinuation from this study treatment
- All subjects must have a life expectancy of at least 12 weeks
- Females of childbearing potential (FCBP) must agree to utilize two reliable forms of contraception simultaneously without interruption for at least 28 days before starting study drug, while participating in the study, and for at least 90 days after study treatment discontinuation
- Males must agree to use a latex condom during any sexual contact with FCBP or a pregnant female, refrain from donating semen or sperm and not to father a child

Exclusion Criteria:
- Patients who have had radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events from agents administered more than 4 weeks earlier
- Patients receiving any other investigational agents.
- Patients who have previously received Romidepsin, Azacitidine, Lenalidomide or Durvalumab or any programmed cell death-1 (PD1) or programmed cell death ligand 1 (PD-L1) inhibitor or participate currently on another clinical trial
- Patients with untreated or uncontrolled brain metastases or leptomeningeal disease
- Presence of other active illnesses
- Any known cardiac abnormalities such as: congenital long QT syndrome; corrected QT interval (QTc interval) ≥ 470 milliseconds. Calculated from 3 ECGs using Fridericia's Correction
- Myocardial infarction within 6 months prior to cycle 1, day 1 (C1D1).
- Other significant ECG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min)
- Symptomatic coronary artery disease (CAD)
- Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions and/or known ejection fraction <40% by multiple gated acquisition scan (MUGA) or <50% by echocardiogram and/or MRI - A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter defibrillator (AICD) - Concomitant use of any drug known to prolong QT interval - Concomitant use of strong CYP3A4 inhibitors - Lactating, pregnant or breast feeding - Patients with any other medical or psychological condition deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results - Diagnosis of immunodeficiency or any condition that requires systemic steroid therapy or other forms of immunosuppressive therapy - Prior thromboembolic events - History of other malignancies - Any uncontrolled active systemic infection - Major surgery within 4 weeks prior to first dose of study drug - Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. - History of stroke or intracranial hemorrhage within 6 months prior to enrollment - History of interstitial lung disease, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis - Unable to swallow oral medication or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction - Concomitant use of warfarin or other Vitamin K antagonists - Known allergy or hypersensitivity to any study drug or any of the study drug excipients - Unwilling or unable to participate in all required study evaluations and procedures. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information. - Current or prior use of immunosuppressive medication within 14 days before the first dose of Durvalumab. - Active or prior documented autoimmune or inflammatory disorders - Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy - History of allogenic organ transplantation - Active infection including tuberculosis - Receipt of live attenuated vaccine within 30 days prior to the first dose of Investigational medicinal product (IMP) - Subject is an employee of the sponsor

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CONTACTS AND LOCATIONS

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Locations

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Germany	Universitätsmedizin Göttingen	Göttingen
Germany	Universitätsklinikum Hamburg-Eppendorf	Hamburg
Germany	Uniklinik Köln	Köln
Germany	Ludwig-Maximilians-Universität München	München

Germany	Klinikum Nürnberg	Nürnberg
Germany	Universitätsklinikum Ulm	Ulm
Germany	Universitätsklinikum Würzburg	Würzburg

Sponsors and Collaborators

GWT-TUD GmbH

Celgene

AstraZeneca

Investigator

Principal Investigator :	Jens Siveke, Prof. Dr.	Institute for Developmental Cancer Therapeutics

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MORE INFORMATION

Responsible Party :	GWT-TUD GmbH
ClinicalTrials.gov Identifier :	NCT04257448
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Studies a U.S. FDA-regulated Drug Product:	No
Studies a U.S. FDA-regulated Device Product:	No
Additional relevant MeSH terms :	*Adenocarcinoma* *Pancreatic Neoplasms*