Combining anti-PD-L1 immune checkpoint inhibitor durvalumab with TLR-3 agonist rintatolimod in patients with metastatic pancreatic ductal adenocarcinoma for therapy efficacy. DURIPANC study.

Published: 09-01-2023
Last updated: 30-01-2025

This study has been transitioned to CTIS with ID 2024-514597-42-00 check the CTIS register for the current data. The primary objective of the safety run-in (phase Ib) is to determine the safety of combination therapy with durvalumab and rintatolimod...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Exocrine pancreas conditions
Study type	Interventional

Summary

ID

NL-OMON56232

Source
ToetsingOnline

Brief title
DURIPANC

Condition

- Exocrine pancreas conditions
- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic pancreatic cancer, metastatic pancreatic ductal adenocarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,AIM Immunotech,Astra Zeneca

Intervention

Keyword: anti PDL-1, Immunotherapy, Pancreatic cancer, TLR-3 agonist

Outcome measures

Primary outcome

The primary objective of the safety run-in (phase Ib) is to determine safety of

combination therapy with durvalumab and rintatolimod.

The primary objective of the phase II trial is to determine the clinical

benefit rate of combination therapy with durvalumab and rintatolimod.

Secondary outcome

The secondary objectives are:

1. To explore the immunogenic effect of combination therapy on the circulating

immune profile.

2. To explore the immunogenic effect of combination therapy on the infiltrating

immune profile.

3. To determine the clinical effect of combination therapy on survival rates

4. To determine the clinical effect of combination therapy on quality of life.

Study description

Background summary

Pancreatic ductal adenocarcinoma (PDAC) is estimated to become the second leading cause of cancer-related death by 2030. Effective management of PDAC is challenged by a combination of late diagnosis, lack of effective screening methods and high risk of early metastasis. Although systemic chemotherapy improves survival, 5-year survival is only 6%. Chemotherapy efficacy is attenuated by innate and acquired drug resistance of tumor cells, a strong desmoplastic reaction that limits local accessibility of drugs and a *cold* tumor microenvironment (TME) with high infiltrating levels of immunosuppressive cells. In PDAC, , increased T cell exhaustion defined by increased PD-1/PD-L1 activity in both peripheral blood and tumor microenvironment, is associated with poor prognosis. Hence the rationale for targeting the PD-1/PD-L1 axis with the aim to release the *brake* and exert an anti-tumor response. In PDAC successful results with Immune Checkpoint Inhibition (ICI) monotherapy are limited and combination therapy with other agents is encouraged; specifically agents that induce dendritic cell priming. We hypothesize that combination therapy of ICI therapy with a toll like receptor 3 (TLR-3) agonist is a potential effective strategy. TLR-3 agonists are hypothesized to increase dendritic cell maturation and cross-priming naïve cytotoxic CD8 T cells while eliminating regulatory T-cell attraction, thereby acting as an immune-boosting agent. We propose that rintatolimod/durvalumab-combination therapy is feasible and may induce synergistic anti-tumor immune responses in PDAC.

Study objective

This study has been transitioned to CTIS with ID 2024-514597-42-00 check the CTIS register for the current data.

The primary objective of the safety run-in (phase Ib) is to determine the safety of combination therapy with durvalumab and rintatolimod. The primary objective of the phase II trial is to determine the clinical benefit rate of combination therapy with durvalumab and rintatolimod. The secondary objective is to explore the immunogenic effect and survival rates after combination therapy.

Study design

exploratory, open-label, single center, phase I-II study. In phase 1 between 9 and max. 18 patients will be included. In the phase II study between 13 and 25 patients will be included.

Intervention

All included patients will receive combination therapy with rintatolimod and durvalumab. Patients will start with rintatolimod 200mg via IV infusion twice per week for a total of 6 weeks (12 doses). Rintatolimod dose will be escalated to 400mg according to a 3+3 DLT design. The first dose of rintatolimod will be

administered preferably 4-6 weeks after the last chemotherapy FOLFIRINOX dose. After two doses of rintatolimod, the first dose of durvalumab 1500mg via IV infusion will be introduced in week 2. Patients will continue to receive 1500 mg durvalumab via IV infusion every 4 weeks for up to a maximum of 48 weeks (up to 12 doses/cycles) with the last administration on week 48 or until confirmed disease progression according to Response Evaluation Criteria in solid Tumors (RECIST 1.1), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Study burden and risks

Patients will receive 12 doses of rintatolimod via IV infusion and a max. of 12 doses durvalumab via IV infusion. In addition, they will undergo additional blood sampling in order to determine tumor-specific immune and tumor marker responses. Intravenous administration of medication and blood sampling can cause bruising or slight short-term discomfort. In previously performed trials, monotherapy with rintatolimod and monotherapy with durvalumab proved to be safe showing a low toxicity profile. Therefore we do not expect any major side-effects of this treatment in our patient population. However, combination treatment with rintatolimod and durvalumab has not been investigated yet, and a synergistic effect can induce unwanted side effects. To determine the safety of combination therapy, a limited number of patients will be included in the safety run-in to determine the RP2D. In addition, to explore the local anti-tumor effect of combination therapy, biopsies will be performed before start and after 12 weeks of treatment in a subset of the included patients.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Doctor Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Doctor Molewaterplein 40
Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Histologically or cytologically (Bethesda 5 or 6) confirmed metastatic pancreatic cancer, as indicated by a definite cytology/histology report.
• Stable disease according to RECIST criteria version 1.1 after at least 8 cycles of chemotherapy (FOLFIRINOX).
• Inclusion <= 6 weeks after stopping FOLFIRINOX.
• An accessible metastatic lesion for histological tissue collection.
• SIII<900 (Systemic Immune-Inflammation Index = ((absolute neutrophil count * platelet count) / absolute lymphocyte count)).
• CA 19.9 <1000kU/L.
• Age >= 18 years at time of study entry.
• Body weight >30 kg.
• WHO performance status of 0-1.
• Adequate renal function (eGFR > 40 ml/min).
• Adequate liver tests (bilirubin <= 1.5 times normal; ALAT/ASAT <= 5 times normal).
• Adequate bone marrow function (WBC > 3.0 x 109/L, platelets > 75 x 109/L , absolute neutrophil count (ANC) >=1.0 × 109 /L and hemoglobin > 5.6 mmol/L.
• Effective contraceptive methods.
• Patient must have a life expectancy of at least 12 weeks.
• 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.
• Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., European Union Data Privacy Directive) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

Exclusion criteria

• Child-Pugh Classification grade B/C.
• Current treatment with immunotherapeutic drugs.
• Previous malignancy (excluding non-melanoma skin cancer, pancreatic neuroendocrine tumor (pNET) <2cm, and gastrointestinal stromal tumor (GIST) <2cm), unless no evidence of disease and diagnosed more than 3 years before diagnosis of pancreatic cancer, or with a life expectancy of more than 5 years from date of inclusion.
• Malignant ascites or pleural effusion.
• Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.
• Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
• An active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or other immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
A. Patients with vitiligo or alopecia;
B. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement;
C. Any chronic skin condition that does not require systemic therapy;
D. Patients without active disease in the last 5 years may be included but only after consultation with the study physician;
E. Patients with celiac disease controlled by diet alone.
• Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 14 days prior to the planned first dose of the study. The following are exceptions to this criterion: 1) Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection), 2) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent and 3) Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
• Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
• Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment.
• Participation in another clinical study with an investigational product

during the last 3 months.
• Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
• Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) <=28 days prior to the first dose of study drug If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca and the investigator.
• Any unresolved toxicity NCI CTCAE Grade >=2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
o Patients with Grade >=2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
o Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
• Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
• Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
• Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
• History of allogenic organ transplantation.
• Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
• History of leptomeningeal carcinomatosis.
• Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with IV contrast of the brain prior to study entry to rule out the presence of brain metastasis.
• Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) >=470 ms.
• Known active hepatitis infection, positive hepatitis C virus (HCV) antibody, hepatitis B virus (HBV) surface antigen (HBsAg) or HBV core antibody (anti-HBc), at screening. Participants with a past or resolved HBV infection (defined as the presence of anti HBc and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Adjust wording as necessary and consider

evaluating at screening for studies with known hepatotoxicity or other relevant requirements.
• Known to have tested positive for human immunodeficiency virus (HIV) (positive HIV 1/2 antibodies) or active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).
• Serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-01-2024
Enrollment:	43
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ampligen
Generic name:	rintatolimod
Product type:	Medicine
Brand name:	IMFINZI
Generic name:	durvalumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-01-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-06-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	23-07-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-514597-42-00
EudraCT	EUCTR2022-003780-23-NL
ClinicalTrials.gov	NCT05927142
CCMO	NL83224.078.22