ElevatION NET-201: An Open-Label Phase II Study to Evaluate the Efficacy and Safety of PDR001 in Patients With Advanced or Metastatic, Well-Differentiated, Non-Functional NET of Pancreatic, Gastrointestinal (GI), or Thoracic Origin or Poorly-Differentiated Gastroenteropancreatic Neuroendocrine Carcinoma (GEP-NEC) Who Have Progressed on Prior Treatment

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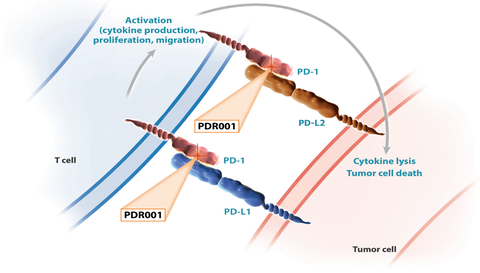
Introduction

- Monoclonal antibody (mAb) inhibitors of immune checkpoints, including anti-programmed cell death protein-1 (PD-1) and its ligands PD-L1/2, have become established treatment options in various solid tumors.[1]
- Although many advances with checkpoint inhibitors have been made in other tumor types, the data generated in neuroendocrine tumors (NETs) are limited.
- PD-1 is a receptor, expressed on activated T cells and other lymphocytes, which negatively regulates T-cell function.[2]
  - Binding of PD-1 by PD-L1 or PD-L2 results in the inhibition of T-cell function, and the protection of tumor cells from attack by cytotoxic T cells[3]
  - Tumors can evade the immune system by upregulating expression of PD-L1[4]
- PD-L1 overexpression has been associated with poorer prognosis in some tumor types.[5-8]
- In GEP-NET tumors PD-L1 expression was found to be significantly associated with high grade tumors (Grade 3).[9]
- In preclinical models, PD-1 blockade has been shown to restore effector T-cell function, leading to T-cell proliferation, interferon-γ secretion, and increased cytolytic function.[10,11]
- PDR001 is a high-affinity, humanized IgG4 antibody directed against PD-1 that blocks the binding of PD-L1 and PD-L2 to PD-1.[12-16] (**Figure 1**).
- In a phase I trial of PDR001 (mAb checkpoint inhibitor targeting PD-1) conducted in patients with multiple solid tumor types, a patient with histologically confirmed metastatic atypical pulmonary carcinoid demonstrated a partial response with (according to RECIST v1.1) resolution of liver and pleural metastases.[16]

Figure 1. Mechanism of Action of PDR001

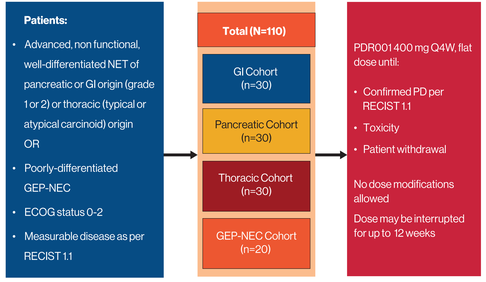


Methods

Study Design

- This is a phase II (NCT02955069), single-arm, open-label, multicenter study in patients with advanced or metastatic, well-differentiated, non functional, NET of pancreatic, gastrointestinal (GI) or throacic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) who have progressed on or after their last treatment (**Figure 2**).
- Patients will receive PDR001 (400 mg, once every 4 weeks) administered via intravenous (IV) infusion over 30 minutes until disease progression, unacceptable toxicity, or patient withdrawal.

Figure 2. Study Design



ECOG, Eastern Cooperative Oncology Group; GEP-NEC, gastroenteropancreatic neuroendocrine carcinoma; GI, gastrointestinal; PD, progressive disease; pNET, pancreatic neuroendocrine tumor; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

Study Endpoints

Primary endpoint

- Overall Response Rate (ORR) per RECIST 1.1 and Blinded Independent Review Committee (BIRC)

Key secondary endpoint

- Duration of Response (DOR) per RECIST 1.1 and BIRC

Additional secondary endpoints

- Disease Control Rate (DCR) per RECIST 1.1 and BIRC
- Time to Response (TTR) per RECIST 1.1 and BIRC
- Progression-free Survival (PFS) per RECIST 1.1 and BIRC
- 1-year and 2-year overall survival rates
- Efficacy endpoints based on immune response criteria per immune-related RECIST and BIRC (irORR, irDOR, irDCR, irTTR, irPFS)
- Changes from baseline in chromogranin A and neuron specific enolase
- Pharmacokinetic (PK) parameters
- Global health status/Quality of Life (QoL) score of the EORTC QLQ-C30 and the index score of the EQ-5D-5L
- Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment
- Frequency and severity of adverse events (AEs)

Key Inclusion Criteria

- Pathologically confirmed, advanced (unresectable or metastatic):
  - Well-differentiated (Grade 1 or Grade 2) based on local pathology report, non-functional NET of GI or pancreatic origin or thoracic (including lung and thymus) origin (typical or atypical carcinoid)
  - Poorly-differentiated GEP-NEC based on local pathology report
- No active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment.
- Patients must have received prior treatment for advanced disease:
- Tumor biopsy material must be provided for all patients for the purpose of biomarkers analysis:
  - Well-differentiated NET: Biopsy material must be provided following the diagnosis of metastatic disease. The tumor sample must be collected from a metastatic site not previously irradiated and should preferably be taken within 6 months but not more than 24 months prior to start of study treatment.
  - Poorly-differentiated GEP-NEC: Biopsy material must be collected from the primary tumor or from a metastatic site not previously irradiated, taken not more than 24 months prior to start of study treatment.

Well-differentiated NET group

Thoracic (lung and thymus origin) cohort

- Thymus origin: at least one prior systemic therapy according to investigator's choice
- Lung origin: at least one prior systemic therapy is required, which must include everolimus

GI cohort

- At least two prior systemic regimens, which must include everolimus

pNET cohort

- At least two prior systemic regimens, which must include everolimus and/or sunitinib.

Poorly-differentiated GEP-NEC group

GEP-NEC cohort

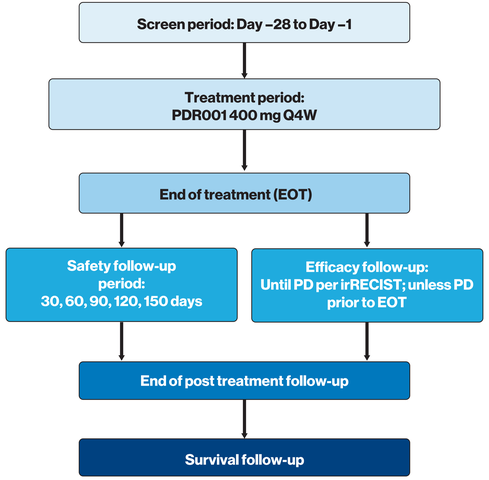
- At least one prior chemotherapy regimen according to Investigator's choice

- Radiological documentation of disease progression:
  - Well-differentiated NET: disease progression while on/or after the last treatment; progression must have been observed within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry). Disease must show evidence of progression based on scans performed not more than one year apart.
  - Poorly-differentiated GEP-NEC: disease progression while on/or after prior treatment
- At least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1.

Key Exclusion Criteria

- Well-differentiated, Grade 3 neuroendocrine tumors; poorly differentiated neuroendocrine carcinoma of any origin (other than GEP-NEC) including NEC of unknown origin, adenocarcinoid, and goblet cell carcinoid
- Pretreatment with interferon-□ as last treatment prior to start of study treatment
- Prior treatment for study indication with:
  - Antibodies or immunotherapy within 6 weeks before the first dose of study treatment
  - PRRT administered within 6 months of the first dose
  - Systemic antineoplastic therapy (including cytotoxic chemotherapy, and toxin immune-conjugates) or any experimental therapy within 14 days or 5 half-lives
  - Tyrosine kinase inhibitors within 14 days or 5 half-lives, before the first dose of study treatment
  - Prior PD-1– or PD-L1–directed therapy
  - Cryoablation, radiofrequency ablation, or trans arterial embolization of hepatic metastases within 2 months before the first dose of study treatment
- History of severe hypersensitivity reactions to other mAb which in the opinion of the investigator may pose an increased risk of a serious infusion reaction
- Known history or current interstitial lung disease or non-infections pneumonitis
- Use of somatostatin analogs or any other medications administered to control active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment

Study Flow

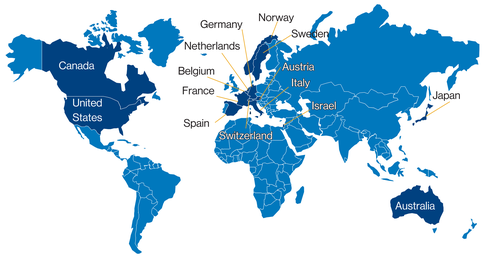


Statistical Analysis

The primary efficacy variable of the study is ORR, defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), as per blinded independent central review. ORR will be evaluated according to RECIST 1.1. ORR will be calculated separately within well-differentiated NET and poorly-differentiated GEP-NEC groups. No formal hypothesis testing will be conducted.

The response rate within each group with 95% two-sided confidence interval (exact method) will be computed.

Study Enrollment



Conclusions

- This phase II, open-label, multicenter study has enrolled patients in United States, Europe, Canada, Australia, Israel, and Japan (NCT02955069) to investigate the role of immunotherapy in NET after prior treatment.

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