NOVARTIS

FRM-7043019

**Sponsor**

Novartis

**Generic Drug Name**

Spartalizumab / PDR001

**Trial Indication(s)**

Metastatic microsatellite stable (MSS) colorectal cancer

**Protocol Number**

CPDR001I2101

**Protocol Title**

ElevatION: CRC-101: A Phase Ib study of PDR001 in combination with bevacizumab and mFOLFOX6 as first line therapy in patients with metastatic microsatellite stable (MSS) colorectal cancer

**Clinical Trial Phase**

Phase IB

**Phase of Drug Development**

Phase III

**Study Start/End Dates**

25-Sep-2017 to 30-Jan-2018

**Reason for Termination**

Novartis terminated the study during the safety run-in phase with only one subject enrolled due to business reasons. The trial termination was unrelated to any safety concerns or anticipated lack of efficacy associated with PDR001.

**Study Design/Methodology**

The study was planned to be a multi-center, open label trial to evaluate the safety, tolerability and efficacy of PDR001 in combination with bevacizumab and mFOLFOX6 in previously untreated adult subjects with metastatic MSS colorectal cancer. The study was planned with two parts: a safety run-in part and an expansion part. However, the study was terminated during the safety run-in phase with only one patient enrolled due to business reasons. The patient received 400mg of PDR001 administered via intravenous infusion once every four weeks, in combination with bevacizumab at 5 mg/kg i.v. plus oxaliplatin 85 mg/$m^2$ i.v., plus leucovorin 400 mg/$m^2$ i.v., plus 5-Flurouracil 400 mg/$m^2$ i.v. bolus, followed by 5-Flurouracil 2400 mg/$m^2$ every two weeks.

**Centers**

1 center in 1 country: United Kingdom

**Objectives:**

**Primary objective(s)**

Safety run-in part: to assess the safety and tolerability of PDR001 in combination with bevacizumab and mFOLFOX6 in previously untreated subjects with metastatic MSS CRC.

Expansion part: to evaluate the efficacy based on overall response rate (ORR) per RECIST v1.1 of PDR001 in combination with bevacizumab and mFOLFOX6 in previously untreated subjects with metastatic MSS CRC.

**Secondary objective(s)**

To evaluate the efficacy of PDR001 in combination with bevacizumab and mFOLFOX6.

To evaluate the safety and tolerability of PDR001 in combination with bevacizumab and mFOLFOX6.

To characterize the pharmacokinetics (PK) of PDR001, bevacizumab and mFOLFOX6 when administered in combination.

To evaluate the prevalence and incidence of immunogenicity of PDR001 and bevacizumab when given in combination with mFOLFOX6.

To assess the overall survival (OS).

**Test Product (s), Dose(s), and Mode(s) of Administration**

PDR001 400 mg every four weeks given as a 30 minute intravenous infusion.

Bevacizumab every two weeks at 5 mg/kg.

Modified FOLFOX6 every two week is chemotherapy combination of oxaliplatin 85 mg/m$^2$ i.v. over two hours, plus leucovorin 400 mg/m$^2$ i.v. over two hours, plus 5-Flurouracil 400 mg/m$^2$ i.v. bolus over 2-4 minutes followed by 5-Flurouracil 2400 mg/m$^2$ over 46 h as continuous infusion. The regimen was repeated every two weeks (Day 1 and Day 15 of each 28-day cycle).

**Statistical Methods**

No analyses were performed since only one subject was enrolled into the study. Data on this subject was listed, and detailed statistical information is not applicable.

This study was planned to be a multi-center, open label, Phase Ib trial to evaluate the safety, tolerability and efficacy of PDR001 in combination with bevacizumab and mFOLFOX6 in previously untreated adult subjects with metastatic MSS colorectal cancer. However, the study was terminated by Novartis during the safety-run-in phase with only one subject enrolled, due to business reasons. The trial termination was unrelated to any safety concerns or anticipated lack of efficacy associated with PDR001. The study plan to start with an eight-week safety run-in exploring, as the primary objective, the safety and tolerability of the combination PDR001 with bevacizumab and mFOLFOX6 and enrolling approximately 6 to 20 subjects. As starting dose, PDR001 was given at a fixed dose of 400 mg i.v. (intravenous) every four weeks in combination with bevacizumab at 5 mg/kg and mFOLFOX6 i.v. every 2 weeks. An expansion part was planned upon completion of the safety run-in part and planned to enroll approximately 92 subjects including those in the safety run-in part.

## Study Population: Key Inclusion/Exclusion Criteria

### Inclusion criteria

- Patients with metastatic MSS colorectal adenocarcinoma. Note: MSI status will be performed locally by an immunohistochemistry (IHC) or PCR based test for eligibility.
- Patients must provide a newly obtained or an archival tumor sample corresponding to CRC diagnosis (primary tumor) with sufficient tissue quality (qualified) for analysis (mandatory)
- Patients must provide a newly obtained tumor tissue sample from a metastatic site (mandatory)
- Patients who are naïve to systemic treatment in metastatic setting. Patients with previous neoadjuvant or adjuvant chemotherapy (that may have included oxaliplatin or investigational VEGF inhibitors) are eligible if the treatment was completed > 12 months before inclusion.
- Patients with the presence of at least one lesion with measurable disease as per RECIST 1.1 guidelines. Lesions in previously irradiated areas should not be considered measurable unless they have clearly progressed since the radiotherapy.
- Patients have an Eastern Cooperative Oncology Group (ECOG) performance status 0-1

### Exclusion criteria

- Patients with MSI-H colorectal adenocarcinoma as defined per local assessment using standard of care testing
- Patients with metastatic disease amenable to be resected with potentially curative surgery
- Patients who have received any systemic treatment for metastatic disease.
- Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PDL2, anti-CTLA-4 antibodies, other checkpoint inhibitors
- Patients who had received radiation within 14 days prior to the first dose of study drug

## Participant Flow Table

Two subjects were screened in the study. Of these, one subject was a screen failure, and the remaining one subject enrolled for the safety run-in and then ended treatment due to disease progression and subsequently withdrew consent during post treatment follow-up.

## Baseline Characteristics

The one subject enrolled was a 66 year-old Caucasian male with a baseline ECOG performance status of 1.

## Summary of Efficacy

No formal efficacy results were reported for this study. For the one subject enrolled, local response assessments were performed. However, no efficacy conclusions can be made given that only one subject was enrolled.

## Summary of Safety

| **Serious adverse events** | PDR+BEV+mFOLFOX6 |
|---|---|
| Total subjects affected by serious adverse events | |
| subjects affected / exposed | 1 / 1 (100.00%) |
| number of deaths (all causes) | 0 |
| number of deaths resulting from adverse events | 0 |
| Blood and lymphatic system disorders | |
| Febrile neutropenia | |
| subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 |
| General disorders and administration site conditions | |
| Pyrexia | |
| subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 |

| **Non-serious adverse events** | PDR+BEV+mFOLFO X6 |
|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 1 / 1 (100.00%) |

| | |
|---|---|
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Stoma complication<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Investigations<br>Weight decreased<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Nervous system disorders<br>Neuropathy peripheral<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Eye disorders<br>Blepharospasm<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 2 |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |

| | |
|---|---|
| Nausea<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Stomatitis<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Vomiting<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 2 |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Musculoskeletal and connective tissue disorders<br>Muscle spasms<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 2 |
| Infections and infestations<br>Candida infection<br>subjects affected / exposed | 1 / 1 (100.00%) |
| occurrences (all) | 1 |

**Other Relevant Findings**

None

**Conclusion:**

No conclusions were drawn from the results of this study regarding the safety and tolerability of PDR001 in combination with bevacizumab and mFOLFOX6 as first line therapy in subjects with metastatic MSS colorectal cancer, as only one subject was enrolled and received the study treatment. Novartis decided to permanently halt recruitment and terminate this study for business reasons. The trial termination was unrelated to any safety concerns or anticipated lack of efficacy associated with PDR001.

**Date of Clinical Trial Report**

10 July 2018