NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Spartalizumab

Trial Indication(s)

Previously treated metastatic microsatellite stable (MSS) colorectal cancer

Protocol Number

CPDR001I2102

Protocol Title

Phase Ib study of PDR001 in combination with regorafenib in adult patients with previously treated metastatic microsatellite stable (MSS) colorectal cancer

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: June 2017 (Actual)
Primary Completion Date: May 2019 (Actual)
Study Completion Date: May 2019 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, open-label, Phase Ib study of the combination spartalizumab and regorafenib in patients with metastatic MSS CRC. The study was designed to evaluate up to two dose levels of regorafenib in combination with spartalizumab given at a fixed-dose, in cohorts of 3-6 evaluable subjects each, to determine the MTD or RP2D for the study combination. It was anticipated that a minimum of 12 subjects would be enrolled in this phase of the study. However, only 10 subjects were enrolled at the first planned dose level (spartalizumab 400 mg + regorafenib 120 mg) and following review of data (cut-off date 25-Oct-2017) at the dose-escalation meeting (DEM) (06-Nov-2017), a decision was made not to proceed with the second dose and permanently halt recruitment and retire the study. Thus, the RP2D of the study treatment was not determined.

Centers

11 centers in 8 countries: Australia(2), Canada(1), Spain(2), Korea, Republic of(1), Netherlands(1), Italy(2), Singapore(1), Israel(1)

6 sites in 5 countries enrolled patients and 1 site had only screen failures: Australia, Canada, Republic of Korea, Israel, Spain.

Objectives:

Primary Objective:

- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of spartalizumab in combination with regorafenib in subjects with metastatic MSS CRC

Secondary Objective:

- To evaluate the safety and tolerability of spartalizumab in combination with regorafenib
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Test Product (s), Dose(s), and Mode(s) of Administration

PDR001 (Spartalizumab) was supplied in 100 mg lyophilisate in vial and was dosed at 400 mg every 4 weeks, given as a 30 minute infusion.
Regorafenib was supplied in 40 mg tablets and was dosed once daily for the first 21 days of a 28-day cycle. The dose was decided by dose decision meeting to be either 120 mg, 80 mg or 160 mg.

Statistical Methods

The adaptive BLRM guided by escalation with overdose control (EWOC) principle was used to make dose recommendations and estimate the MTD/ RP2D during the dose-escalation part of the study for spartalizumab in combination with regorafenib. The dose decision was guided by the EWOC principle.A dose might only be used for newly enrolled subjects if the risk of excessive toxicity at that dose was less than 25%. The Dose-limiting toxicities (DLTs) were listed based on the CTCAE version 4.03 and the type of AE. The dose determining analysys set (DDS) was used for these listings.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria:
1. Patients with metastatic colorectal adenocarcinoma.
2. Patients must provide a newly obtained or an archival tumor sample corresponding to CRC diagnosis (primary tumor) with sufficient tissue quality (qualified) for analysis
3. Patients must provide a newly obtained tumor tissue sample from a metastatic site
4. Patients with the presence of at least one lesion with measurable disease as per RECIST
5. Patients previously treated with two prior regimen as per standard of care and have experienced disease progression (including - VEGF and EGFR targeted therapies (if KRAS wild).
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0-1

Key exclusion criteria:
1. Patients with MSI-H colorectal adenocarcinoma as defined per local assessment using standard of care testing
2. Patients with metastatic disease amenable to be resected with potentially curative surgery
3. Patients who have had chemotherapy, radiation, or biological cancer therapy within 14 days prior to the first dose of study treatment
4. Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PDL2, anti-

CTLA-4 antibodies, other checkpoint inhibitors

Participant Flow Table

Overall Study

	PDR001 400mg + REG 120mg	Total
Arm/Group Description	Subjects with metastatic MSS CRC received a combination of spartalizumab (PDR001) and regorafenib (REG).	
Started	10	10
Completed	0	0
Not Completed	10	10
Progressive Disease	9	9
Adverse Event	1	1

Baseline Characteristics

	PDR001 400mg + REG 120mg	Total
Arm/Group Description	Subjects with metastatic MSS CRC received a	

	combination of spartalizumab (PDR001) and regorafenib (REG).	
Number of Participants [units: participants]	10	10
Age, Customized (units: Participants)		
In utero	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0
Newborns (0-27 days)	0	0
Infants and toddlers (28 days-23 months)	0	0
Children (2-11 years)	0	0
Adolescents (12-17 years)	0	0
Adults (18-64 years)	5	5
From 65-84 years	5	5
85 years and over	0	0
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)		
Female	0	0
Male	10	10
Age Continuous (units: years) Mean ± Standard Deviation		
	62.2±11.23	

Race/Ethnicity, Customized (units: participants)		
Caucasian	8	8
Asian	1	1
Other*	1	1

*Other = Hispanic/Latino

Summary of Efficacy

Primary Outcome Result(s)

Incidence of dose limiting toxicities (DLTs) during the first 8 weeks of treatment

(Time Frame: first 8 weeks of treatment)

	PDR001 400mg + REG 120mg
Arm/Group Description	Subjects with metastatic MSS CRC received a combination of spartalizumab (PDR001) and regorafenib (REG).
Number of Participants Analyzed [units: participants]	9
Incidence of dose limiting toxicities (DLTs) during the first 8 weeks of treatment (units: Participants)	

1

Secondary Outcome Result(s)

None

Summary of Safety

Safety Results

All-Cause Mortality

	PDR001 400mg + REG 120mg N = 10
Arm/Group Description	Subjects with metastatic MSS CRC received a combination of spartalizumab (PDR001) and regorafenib (REG).
Total participants affected	1 (10.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus up to 150 days post treatment, up to maximum duration of 16.5 months
Additional Description	AE description; Any sign or symptom that occurs during the study treatment plus the # days post treatment

Source Vocabulary for Table Default	MedDRA 22.0
Assessment Type for Table Default	Systematic Assessment

	PDR001 400mg + REG 120mg N = 10
Arm/Group Description	Subjects with metastatic MSS CRC received a combination of spartalizumab (PDR001) and regorafenib (REG).
Total participants affected	8 (80.00%)
Blood and lymphatic system disorders	
Anaemia	1 (10.00%)
Cardiac disorders	
Myocardial infarction	1 (10.00%)
Gastrointestinal disorders	
Colitis	2 (20.00%)
Intestinal obstruction	1 (10.00%)
Large intestinal obstruction	1 (10.00%)

Lower gastrointestinal haemorrhage	1 (10.00%)
Rectal haemorrhage	1 (10.00%)
Small intestinal obstruction	1 (10.00%)
General disorders and administration site conditions	
Pyrexia	1 (10.00%)
Infections and infestations	
Pneumonia	1 (10.00%)
Injury, poisoning and procedural complications	
Femur fracture	1 (10.00%)
Metabolism and nutrition disorders	
Dehydration	1 (10.00%)
Musculoskeletal and connective tissue disorders	
Back pain	1 (10.00%)
Renal and urinary disorders	
Nephritis	1 (10.00%)
Skin and subcutaneous tissue disorders	
Rash	1 (10.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus up to 150 days post treatment, up to maximum duration of 16.5 months
Additional Description	AE description; Any sign or symptom that occurs during the study treatment plus the # days post treatment
Source Vocabulary for Table Default	MedDRA 22.0
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	PDR001 400mg + REG 120mg N = 10
Arm/Group Description	Subjects with metastatic MSS CRC received a combination of spartalizumab (PDR001) and regorafenib (REG).
Total participants affected	10 (100.00%)
Blood and lymphatic system disorders	
Anaemia	4 (40.00%)
Lymphopenia	2 (20.00%)
Thrombocytopenia	1 (10.00%)
Cardiac disorders	
Pericardial effusion	1 (10.00%)

Endocrine disorders	
Hypothyroidism	1 (10.00%)
Eye disorders	
Eye pain	1 (10.00%)
Photopsia	1 (10.00%)
Vision blurred	1 (10.00%)
Gastrointestinal disorders	
Abdominal pain	4 (40.00%)
Abdominal pain lower	1 (10.00%)
Constipation	1 (10.00%)
Diarrhoea	3 (30.00%)
Dyspepsia	1 (10.00%)
Gastrointestinal inflammation	1 (10.00%)
Glossodynia	1 (10.00%)
Large intestinal obstruction	1 (10.00%)
Nausea	1 (10.00%)
Proctalgia	1 (10.00%)
Rectal discharge	2 (20.00%)
Rectal haemorrhage	1 (10.00%)
Stomatitis	2 (20.00%)
Vomiting	5 (50.00%)
General disorders and administration site conditions	

Asthenia	3 (30.00%)
Chills	1 (10.00%)
Fatigue	4 (40.00%)
Gait disturbance	1 (10.00%)
Hernia	1 (10.00%)
Influenza like illness	1 (10.00%)
Mucosal inflammation	1 (10.00%)
Oedema peripheral	3 (30.00%)
Pain	1 (10.00%)
Pyrexia	3 (30.00%)
Hepatobiliary disorders	
Hyperbilirubinaemia	1 (10.00%)
Jaundice	1 (10.00%)
Infections and infestations	
Pneumonia	2 (20.00%)
Upper respiratory tract infection	1 (10.00%)
Urinary tract infection	1 (10.00%)
Injury, poisoning and procedural complications	
Fall	1 (10.00%)
Gastrointestinal stoma complication	1 (10.00%)
Head injury	1 (10.00%)
Inflammation of wound	1 (10.00%)

Pelvic organ injury	1 (10.00%)
Investigations	
Aspartate aminotransferase increased	1 (10.00%)
Blood bilirubin increased	2 (20.00%)
Blood creatinine increased	1 (10.00%)
Blood thyroid stimulating hormone increased	1 (10.00%)
Brain natriuretic peptide increased	1 (10.00%)
Gamma-glutamyltransferase increased	1 (10.00%)
Lymphocyte count decreased	1 (10.00%)
Transferrin saturation decreased	1 (10.00%)
Weight decreased	5 (50.00%)
Metabolism and nutrition disorders	
Cachexia	1 (10.00%)
Decreased appetite	5 (50.00%)
Hyperglycaemia	1 (10.00%)
Hypoalbuminaemia	2 (20.00%)
Hypocalcaemia	1 (10.00%)
Hypokalaemia	2 (20.00%)
Iron deficiency	1 (10.00%)

Musculoskeletal and connective tissue disorders	
Back pain	1 (10.00%)
Muscle spasms	2 (20.00%)
Muscular weakness	1 (10.00%)
Musculoskeletal chest pain	1 (10.00%)
Pain in extremity	1 (10.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Neurofibroma	1 (10.00%)
Seborrhoeic keratosis	1 (10.00%)
Nervous system disorders	
Headache	1 (10.00%)
Paraesthesia	1 (10.00%)
Tremor	1 (10.00%)
Psychiatric disorders	
Confusional state	1 (10.00%)
Insomnia	2 (20.00%)
Renal and urinary disorders	
Haematuria	1 (10.00%)
Nephritis	1 (10.00%)
Pollakiuria	2 (20.00%)
Urinary incontinence	1 (10.00%)

Respiratory, thoracic and mediastinal disorders	
Cough	2 (20.00%)
Pleural effusion	1 (10.00%)
Productive cough	1 (10.00%)
Sinus pain	1 (10.00%)
Skin and subcutaneous tissue disorders	
Decubitus ulcer	1 (10.00%)
Dry skin	1 (10.00%)
Erythema	1 (10.00%)
Erythema multiforme	1 (10.00%)
Palmar-plantar erythrodysaesthesia syndrome	6 (60.00%)
Pruritus	1 (10.00%)
Rash	4 (40.00%)
Rash generalised	1 (10.00%)
Urticaria	1 (10.00%)
Vascular disorders	
Hypertension	4 (40.00%)

Other Relevant Findings

None

Conclusion:

The aim of this study was to evaluate the combination of spartalizumab and regorafenib in previously treated patients with metastatic microsatellite stable colorectal cancer (MSS CRC). The primary objective of this study was to determine the maximum tolerated dose (MTD and/or recommended phase II dose (RP2D) of spartalizumab in combination with regorafenib in subjects with metastatic microsatellite stable colorectal cancer. Novartis decided not to move forward and to halt recruitment and retire the study after completion of the Dose Escalation Meeting. No formal efficacy analysis was conducted for this study.

The safety results indicated that the majority of the Adverse Events (AEs) could be successfully managed with the existing AE management guidelines used in this disease setting. There were no deaths attributed to the study treatment. The one on-treatment death was due to disease progression. The overall safety profile was consistent with prior experience with spartalizumab.

The pattern of the most frequent adverse events of grade 3 or higher related to regorafenib was similar to that observed in prior regorafenib clinical studies, including hand-foot skin reaction (palmar-plantar erythrodysaesthesia syndrome), fatigue, hypertension, diarrhea among others. Those adverse events were manageable with dose interruption and/or reduction and additional therapy. Overall, the safety profile of regorafenib in this study was consistent with previous clinical experience with tyrosine-kinase inhibitor class in a similar disease setting. However, 7 out of 10 patients were on 0-80 mg of regorafenib raising concerns about longer-term tolerability and ability to maximize to higher dose on that combination.

At the time of the data cut-off (25 Oct 2017), the AEs observed in 2 patients did not meet the protocol definition criteria for DLT during the first 8 weeks of treatment; however, they led to regorafenib dose reduction to less than 50% of the initial recommended dose (120mg), and therefore were considered DLTs for clinical reasons.

Overall, on treatment AEs leading to dose adjustment and/or interruptions were reported in 8 subjects (80.0%) of which 7 subjects (70.0%) experienced at least one grade ≥3 CTCAEs. A total of 8 subjects (80%) experienced at least one SAE: 7 subjects (70%) experienced at least one on treament SAE of which six subjects experienced treatment related SAE and 1 subject experienced a SAE during the extended safety follow-up (up to 150 days post treatment). No fatal SAE were reported.

The investigators endorsed that regorafenib 120 mg in combination with PDR001 400 mg Q4W was not tolerable. As a consequence the 160 mg regorafenib + PDR001 400 mg Q4W cohort did not start.

In addition, changes in the Novartis development plan for spartalizumab corroborated to not pursue the cohort regorafenib 80mg + PDR001 400mg Q4W. Therefore, Novartis decided to permanently halt the recruitment into the CPDR001I2102 study.

In conclusion, the reason to terminate the trial and not move to the higher combination dose, was based on the safety review, numerous dose interruptions and adjustments for the 10 patients on dose level one (spartalizumab 400 mg + regorafenib 120 mg),and also the changes in the spartalizumab clinical development plan. Therefore, Novartis decided to permanently halt the recruitment into the CPDR001I2102 study.

Date of Clinical Trial Report

Final Published CSR: 1 Oct 2019