Clinical Study Report Synopsis	
Drug Substance	Novel oncology therapies: durvalumab (MEDI4736) and oleclumab (MEDI9447)
Study Code	D910CC00001
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A Phase Ib/II, Open-label, Multicenter Study of Novel Oncology Therapies in Combination with Chemotherapy and Bevacizumab as First-line Therapy in Metastatic Microsatellite-stable Colorectal Cancer (COLUMBIA-1)

Study dates: First subject enrolled: 13 September 2019
Date of early study termination: 17 February 2022
The analyses presented in this report are based on a clinical data lock date of 19 May 2023

Phase of development: Clinical pharmacology (I)/Therapeutic exploratory (II)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Rationale for submitting an abbreviated clinical study report

Study D910CC00001 was designed to determine if novel oncology therapies plus standard of care (FOLFOX [folinic acid (leucovorin), 5-fluorouracil, oxaliplatin] plus bevacizumab) would demonstrate superior antitumor efficacy to standard of care alone in subjects with first-line (1L) metastatic microsatellite-stable (MSS) colorectal cancer (CRC). CCI [redacted]

Study centers

Participants were screened and enrolled for this study at 20 sites globally: US (10), Canada (1), Spain (4), France (2), and Australia (3).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1 - **Safety:** To evaluate the safety and tolerability profile of FOLFOX + bevacizumab + novel oncology therapy combinations	Incidence of AEs, SAEs, DLTs, laboratory findings, and vital signs
Part 2 - **Efficacy:** To compare the efficacy of FOLFOX + bevacizumab + novel oncology therapy combinations versus FOLFOX + bevacizumab	OR per RECIST v1.1
Secondary	
Part 1 - **Efficacy:** To investigate the preliminary antitumor activity of FOLFOX + bevacizumab + novel oncology therapy combinations	Assessments of antitumor activity include OR, BOR, DoR, DC, PFS-12, and PFS as assessed by RECIST v1.1 and OS
Part 2 - **Safety:** To evaluate the safety and tolerability profile of FOLFOX + bevacizumab + novel oncology therapy combinations	Incidence of AEs, SAEs, laboratory findings, and vital signs
Part 2 - **Efficacy:** To compare the efficacy of FOLFOX + bevacizumab + novel oncology therapy combinations versus FOLFOX + bevacizumab	Assessment of antitumor activity include BOR, DoR, DC, PFS-12, and PFS as assessed by RECIST v1.1 and OS
Part 1 and 2 - **Pharmacokinetics:** To describe the PK of novel agents **Part 1** - **Pharmacokinetics:** To describe the PK of bevacizumab	**Part 1 and 2:** PK (drug concentration) for novel agents **Part 1:** PK (drug concentration) for bevacizumab
Part 1 and 2 - **Immunogenicity:** To describe the immunogenicity of applicable novel agents **Part 1** - **Immunogenicity:** To describe the immunogenicity of bevacizumab	**Part 1 and 2:** Incidence of ADA to applicable novel agents **Part 1:** Incidence of ADA to bevacizumab

Exploratory endpoints are not reported in this abbreviated CSR. For the planned exploratory objectives and endpoints, see Section 2.3 of the CSP in Appendix 16.1.1.

ADA = antidrug antibody; AE = adverse event; BOR = best overall response; CSP = clinical study protocol; CSR = clinical study report; DC = disease control; DLT = dose-limiting toxicity; DoR = duration of response; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; OR = objective response; OS = overall survival; PFS = progression-free survival; PFS-12 = progression-free survival at 12 months; PK = pharmacokinetic(s); RECIST v1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; SAE = serious adverse event.

Study design

Study D910CC00001 was a Phase Ib/II, open-label, multicenter, randomized, multidrug platform study to evaluate the safety and efficacy of standard of care (FOLFOX plus bevacizumab) in combination with novel oncology therapies (durvalumab and oleclumab) in subjects with 1L metastatic MSS-CRC. The study was designed to concurrently evaluate potential novel combinations with clinical promise using a 2-part approach. Part 1 was a Phase Ib study of safety, and Part 2 was a Phase II study of efficacy and safety. The study arms are

defined in Table S2, and regimens are described in Section 3.1.2 of the clinical study protocol (CSP) (see Appendix 16.1.1 of the abbreviated CSR).

Following a screening period of up to 28 days, subjects were centrally assigned (Part 1) or randomized (Part 2) to one of the open study arms.

Table S2 Study Arms and Treatments

Part	Arm	Study Treatment
1	S1	FOLFOX + bevacizumab + durvalumab + oleclumab
CCI [redacted]		

E = experimental; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; S = safety run-in.

Target subject population and sample size

Male and female subjects ≥ 18 years of age with metastatic MSS-CRC who had not received prior treatment in the recurrent/metastatic setting (subjects treated with prior adjuvant chemotherapy or radiochemotherapy could have been accepted so long as progression had not occurred within 6 months of completing the adjuvant regimen).

In Part 1, a minimum of 6 subjects (and up to 12 subjects per dose level of novel agent) may have been enrolled to complete the safety run-in. The number of subjects to be enrolled was dependent upon the toxicities observed during the conduct of the study.

CCI [redacted]

Investigational product and comparator(s): dosage, mode of administration and batch numbers

FOLFOX plus bevacizumab: administered as outlined in the CSP per National Comprehensive Cancer Network and European Society for Medical Oncology guidelines; 5-fluorouracil was administered as infusion only, with no bolus.
Durvalumab (MEDI4736): CCI [redacted] intravenously (IV) CCI [redacted]
Oleclumab (MEDI9447): CCI [redacted] IV CCI [redacted] starting on Cycle 5, Day 1

Batch numbers are provided in Appendix 16.1.6 of the abbreviated CSR.

Duration of treatment

In both study parts, study treatment was to be administered until disease progression or any discontinuation criteria were met. CCI [redacted]

Statistical methods

See Section 4.8 of the CSP in Appendix 16.1.1 of the abbreviated CSR and the Statistical Analysis Plan in Appendix 16.1.9 of the abbreviated CSR.

Study population

The first subject was enrolled onto the study on 13 September 2019 and the last subject last visit was on 10 October 2022. The results presented in this abbreviated CSR are based on a clinical data lock date of 19 May 2023.

Across all parts of the study, a total of 83 subjects were screened (ie, informed consent was signed). There were 22 screen failures, of which 16 subjects did not meet inclusion and/or met exclusion criteria, 3 subjects withdrew consent, and 3 subjects failed for other reasons.

Seven subjects were assigned and received treatment in Part 1. The most common reason for treatment discontinuation during the study was progressive disease for all treatments except oxaliplatin, for which all discontinuations were due to adverse events (AEs). At the time of final analysis (data cutoff [DCO] 19 May 2023), 4 (57.1%) subjects had died during Part 1 of the study (3 [42.9%] due to disease under investigation and 1 [14.3%] due to other cause) and the remaining 3 (42.8%) subjects discontinued from the study due to sponsor decision.

Fifty-four subjects were randomized in Part 2 (27 subjects were assigned to the control [C1] arm and 27 subjects were assigned to the experimental [E1] arm) and 26 subjects received treatment in each study arm. In both study arms, the most common reason for discontinuation was progressive disease for all treatments with the exception of oxaliplatin, for which AEs were the most common reason for discontinuation. At the DCO, 21 (40.4%) treated subjects had died during Part 2 of the study (18 [34.6%] due to disease under investigation and 3 [5.8%] due to other causes). Adverse events contributing to deaths were COVID-19, intestinal perforation, peritonitis, and sepsis (1 [1.9%] subject, each).

Overall, 6 (10.2%) subjects decided to withdraw from the study, 2 (3.4%) subjects were lost to follow-up, and the remaining 26 (44.1%) subjects discontinued from the study due to other reasons (mostly due to sponsor decision).

Summary of efficacy results

The primary efficacy endpoint for Part 2 is objective response (OR) per Response Evaluation Criteria for Solid Tumors version 1.1. Objective response rate (ORR) is defined as the proportion of subjects with a confirmed complete response or partial response. The secondary

endpoints for Part 2 include antitumor response (best overall response [BOR], duration of response [DoR], and disease control [DC]) and survival (progression-free survival [PFS], PFS at 12 months [PFS-12], and overall survival [OS]).

- The confirmed ORR was 61.5% (95% confidence interval [CI], 40.6%-79.8%) in Arm E1 (N = 26) compared with 46.2% (95% CI, 26.6%-66.6%) in Arm C1 (N = 26).
- One (3.8%) subject achieved a complete response in Arm C1.
- There was no improvement in PFS or PFS-12 in Arm E1 compared with Arm C1.

Summary of safety results

Part 1

- The median duration of exposure in subjects was around 44 weeks for durvalumab, oleclumab, and bevacizumab, around 56 weeks for folinic acid and 5-fluorouracil, and 25 weeks for oxaliplatin.
- All subjects had treatment-emergent adverse events (TEAEs).
  - Grade ≥ 3 TEAEs occurred in 6 (85.7%) subjects.
  - The most common TEAEs were diarrhoea, fatigue, paraesthesia, and peripheral sensory neuropathy (5 [71.4%] subjects each), neutrophil count decreased (4 [57.1%] subjects), constipation and stomatitis (3 [42.9%] subjects each), and nausea, rectal haemorrhage, pyrexia, aspartate aminotransferase increased, weight decreased, weight increased, dehydration, dysgeusia, and proteinuria (2 [28.6%] subjects each).
- There were no fatal TEAEs in Part 1.
- One (14.3%) subject experienced serious adverse events (SAEs) (colitis and large intestine perforation). The SAE of colitis was judged by the investigator to be causally related to durvalumab and oleclumab.
- The most common treatment-related AE for durvalumab and oleclumab was pyrexia (2 [28.6%] subjects for both treatments).
- The most common treatment-related AEs for the standard-of-care therapies were neutrophil count decreased, fatigue, diarrhoea, stomatitis, peripheral sensory neuropathy, and paraesthesia.

Part 2

- The median duration of exposure in subjects was similar for both study arms, and for all study treatments (medians range, 31.3-36.8 weeks) except for oxaliplatin with 22.0-23.2 weeks.
- All subjects had TEAEs.
  - Grade ≥ 3 TEAEs occurred in 65.4% of subjects in Arm E1 and in 80.8% of subjects in Arm C1.

  - The most common TEAEs were diarrhoea (53.8% in Arm E1 vs 46.2% in Arm C1), nausea (46.2% vs 50.0%), constipation (46.2% vs 34.6%), stomatitis (30.8% vs 19.2%), fatigue (42.3% vs 38.5%), decreased appetite (30.8% vs 19.2%), dysgeusia (15.4% vs 30.8 %), paraesthesia (19.2% vs 26.9%), and peripheral sensory neuropathy (38.5% vs 42.3%).

- Fatal TEAEs, all unrelated to the study treatments, were observed in 3 subjects in Arm E1 (sepsis, peritonitis, and intestinal perforation) and one subject in the Arm C1 (COVID-19).
- Overall, 19 (36.5%) subjects experienced SAEs (46.2% in Arm E1 and 26.9% in Arm C1).
  - One (1.9%) subject had a durvalumab-related SAE (pyrexia).
  - Two (3.8%) subjects had oleclumab-related SAEs (pyrexia and pulmonary embolism).
  - Two (3.8%) subjects had 5-fluorouracil-related SAEs (ventricular tachycardia, bursitis, and epistaxis).
  - Four (7.7%) subjects had bevacizumab-related SAEs (large intestine perforation, peritonitis, bursitis, epistaxis, and pulmonary embolism).
- The most common treatment related AEs for durvalumab were fatigue (6 [23.1%] subjects), nausea (5 [19.2%] subjects), diarrhoea (4 [15.4%] subjects), and lipase increased (3 [11.5%] subjects). The most common treatment-related AEs for oleclumab were fatigue (6 [23.1%] subjects), diarrhoea (4 [15.4%] subjects), and nausea and rash (3 [11.5%] subjects each).
- The most common treatment related AEs for the standard-of-care therapies were nausea, diarrhoea, fatigue, dysgeusia, peripheral sensory neuropathy, stomatitis, vomiting, neutrophil count decreased, platelet count decreased, decreased appetite, paraesthesia, temperature intolerance, neuropathy peripheral, and epistaxis.

Conclusion

Observed efficacy did not favor further investigation of the novel study drug combination. There are no plans to move forward with the specific drug combination used in this study.