2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsors:
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Servier R&D Ltd, Sefton House, Sefton Park, Bell Hill, Stoke Poges, Slough, Berkshire, SL2 4JS - United Kingdom</td><td rowspan="2">(For National Authority Use only)</td></tr>
<tr><td colspan="2">Test drug
Name of Finished Product:
LONSURF®
Name of Active Ingredient:
S95005 (TAS-102): trifluridine (FTD) and tipiracil hydrochloride (TPI)</td></tr>
<tr><td>Individual Study Table Referring to Part of the Dossier</td><td>Volume:</td><td>Page:</td></tr>
<tr><td colspan="3">Title of study: Phase I dose-escalation of S95005 (TAS-102) in combination with oxaliplatin in metastatic colorectal cancer
Protocol No.: CL1-95005-001
EudraCT No.: 2015-004894-34
The description of the study protocol given hereafter includes the modifications of the five substantial amendments to the protocol.</td></tr>
<tr><td colspan="3">Main Investigator
[redacted]</td></tr>
<tr><td colspan="3">Study countries:
Seven countries included 78 patients: France (25 patients), Spain (21 patients), Italy (12 patients), Hungary (7 patients), Germany (6 patients), United Kingdom (4 patients) and Austria (3 patients).</td></tr>
<tr><td colspan="3">Publication (reference):
Not Applicable</td></tr>
<tr><td colspan="2">Studied period:
Initiation date: 09 May 2016
Completion date: 07 April 2020</td><td>Phase of development of the study:
Phase I</td></tr>
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Objectives:
Primary Objectives:

- Assess the safety and tolerability of S95005 given in combination with oxaliplatin in patients with metastatic colorectal cancer (mCRC) in terms of maximum tolerated doses (MTDs) and dose-limiting toxicities (DLTs) for each dosing tested.
- Determine the recommended dose (RD) of S95005 in combination with oxaliplatin.

Secondary Objectives:

- Assess the pharmacokinetic (PK) profile of S95005 (trifluridine (FTD) and tipiracil hydrochloride (TPI)), oxaliplatin, and their metabolites.
- Investigate the safety profile of S95005 given in combination:
  - With oxaliplatin and bevacizumab.
  - With oxaliplatin and nivolumab.
- Document any preliminary antitumour activity of S95005, in combination:
  - With oxaliplatin.
  - With oxaliplatin and bevacizumab.
  - With oxaliplatin and nivolumab.

In terms of:
- Objective response rate (ORR).
- Duration of response (DR).
- Progression-free survival (PFS).
- Overall survival (OS).

using revised Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1, 2009)

- Assess the ability of PDL-1 expression and density of CD8 Tumour infiltrating Lymphocytes (TILs) to predict response in tumour biopsies, in patients treated with S95005 in combination with oxaliplatin and nivolumab.

Exploratory objectives

- Dose escalation part and expansion part for the cohort bevacizumab (cohort A)

Evaluate the biomarkers potentially predictive of response and resistance to S95005 given in combination with oxaliplatin with or without bevacizumab using blood samples.

- Expansion part for the cohort nivolumab (cohort B)

Evaluate the pharmacodynamics biomarkers and biomarkers potentially predictive of response to S95005 given in combination with oxaliplatin and nivolumab using blood samples and tumour biopsies.

Methodology:
Phase I, international, multicentre, open-label, non-randomised, dose-escalation study of S95005 in combination with oxaliplatin in patients with mCRC, who have been pre-treated by at least one line of standard chemotherapy. The expansion part followed with the addition of bevacizumab (cohort A) or nivolumab (cohort B) to the combination of S95005 with oxaliplatin at the RD.

The study was conducted in 2 parts:

- A dose-escalation part to determine the MTD of S 95005 in combination with oxaliplatin.
  Patients enrolled in the dose-escalation part could receive bevacizumab in addition to S95005 and oxaliplatin when the RD of S95005 plus oxaliplatin was confirmed. The addition of bevacizumab was done at the investigator's discretion subject that they met inclusion and non-inclusion criteria related to bevacizumab.
- An expansion part to evaluate the safety, PK, and preliminary efficacy of S95005 in combination with oxaliplatin and either bevacizumab or nivolumab. The expansion part was divided into 2 cohorts:
  - **Cohort A:** up to 35 evaluable patients received bevacizumab (5 mg/kg IV) in addition to the combination of S95005 and oxaliplatin administered at the RD.
  - **Cohort B:** up to 35 evaluable patients received nivolumab (3 mg/kg IV) in addition to the combination of S95005 and oxaliplatin administered at the RD.

Safety review in expansion cohorts:
For each cohort (A and B), an overall safety review was held independently once 6 patients had completed their 2nd treatment cycle with the triple combination. If the triple combination was well tolerated, enrolment of 9 additional patients to receive the triple combination was allowed.

This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: up to 94 evaluable patients including up to 24 evaluable patients in the dose-escalation part and up to 35 additional evaluable patients in each cohort (A and B) in the expansion part.
Included: 78 patients including 24 patients in the dose-escalation part and 54 patients in the expansion part.

Diagnosis and main criteria for inclusion:
Patients were males or females aged 18 years or older old with histologically confirmed mCRC pre-treated by at least one line of standard chemotherapy for metastatic disease. Patients were required to have Eastern an Cooperative Oncology Group (ECOG) performance status of 0-1, adequate bone marrow, liver and kidney function and at least one measurable metastatic lesion during the expansion part (per revised RECIST version 1.1).
In addition, patients who received nivolumab (cohort B) had to have a confirmed MSS status.

Test drug:
Each treatment cycle lasted for 14 consecutive days. The test drugs were administered as follows:

- S95005: orally BID (twice a day) at different doses (25 mg/m²/dose; 30 mg/m²/dose and 35 mg/m²/dose), within 1 hour after completion of morning and evening meals, from Day 1 through Day 5. This was followed by a recovery period of 9 days beginning on Day 6 through Day 14.
- Oxaliplatin: 2-hour IV infusion at 85 mg/m² or 65 mg/m² on Day 1 of each treatment cycle. The start of infusion was concomitant with the morning administration of S95005 at Day 1.
- Bevacizumab: 5 mg/kg, IV on Day 1 at each treatment cycle.
- Nivolumab: 3 mg/kg, IV on Day 1 at each treatment cycle.

Batch numbers:

- S95005 15 mg: [redacted]; S95005 20 mg: [redacted],
- Oxaliplatin: [redacted],
- Bevacizumab 4 mL: [redacted]; Bevacizumab 16 mL: [redacted]
- Nivolumab 4 mL: [redacted]; Nivolumab 16 mL: [redacted]

During the dose-escalation part, patients were allocated to sequential dose-level cohorts according to the following scheme:

Dose-Level Cohort	S 95005 (mg/m^2) Day 1-5 (twice daily)	Oxaliplatin (mg/m^2) Day 1	Number of patients per Dose-Level
1	25	85	3 to 6
2	30	85	3 to 6
3	35	85	3 to 6
1’	25	65	3 to 6
2’	30	65	3 to 6
3’	35	65	3 to 6

Three patients were initially enrolled into Dose-Level 1 cohort:

- If none of the 3 first patients treated at this dose-level experienced a DLT during cycle 1 or 2, 3 new patients were enrolled into Dose-Level 2.
- If more than 1 of the 3 first patients enrolled into Dose-Level 1 experienced a DLT during cycle 1 or 2, level was de-escalated to Dose-Level 1’.
- If 1 of the 3 first patients enrolled into Dose-Level 1 experienced a DLT during cycle 1 or 2, an additional 3 patients were enrolled at the same dose-level. If 1 or more of the additional 3 patients experienced a DLT during cycle 1 or 2, level was de-escalated to Dose-level 1’. If none of the additional 3 patients experienced a DLT during cycle 1 or 2, 3 new patients were enrolled into Dose-Level 2.
- In case of no DLT observed into Dose-Level 1’, the dose level 2’ was explored. If more than 1 patient observed DLT at dose level 2’, the dose level 1’ was considered as MTD.

This enrolment scheme was followed for all subsequent cohorts.

The MTD was defined as the highest dose-level at which less than 33% of the evaluable patients treated experienced a DLT during cycle 1 or 2 of treatment. Once the MTD was established, 7 additional patients were enrolled to generate further safety data of S 95005 in combination with oxaliplatin and to define the RD.

Comparator:
Not applicable

Duration of treatment:
Patients were treated with S95005 in combination with oxaliplatin and either bevacizumab or nivolumab until radiological evidence of disease progression, the occurrence of unacceptable toxicity (discontinuation secondary to adverse event), withdrawal of patient's consent or at the investigator's discretion. In the nivolumab cohort, the investigator could continue the treatment after radiological progression in case he/she believed that there was a clinical benefit for the patient.

A patient was considered discontinued from the study treatment when:

- Treatment with S95005 was discontinued in the dose-escalation part or in the Cohort A.
- Treatment with S95005 and nivolumab was discontinued in the Cohort B.

Criteria for evaluation:
Efficacy measurements:
Tumour assessments were performed at baseline, every 4 cycles throughout the study and at the withdrawal visit based on revised RECIST version 1.1. The date of disease progression and/or the date of death was collected for patients who withdrew from the study for a reason other than disease progression.
Dosage of Carcinoembryonic Antigen (CEA) was performed (pre-dose) at baseline, at C2D1, C3D1, C5D1, then every 4 cycles and at the withdrawal visit.

Safety measurements:
Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and Levi grading (for peripheral sensory neuropathy).
Other safety assessments: physical examination including clinical neurological examination, ECOG PS, vital signs and blood laboratory tests.

Pharmacokinetic measurements:
See PK report included in Appendix 16.4 of this clinical study report.

Biomarkers measurements:
For the cohort nivolumab (cohort B) in expansion part: newly obtained tumour biopsy performed during baseline period and at the end of Cycle 4 were used for determining potential predictive and pharmacodynamics biomarkers including microsatellite instability status, tumour infiltrating lymphocyte characteristics comprising CD8 TILs density, myeloid cells in tumour microenvironment, immune cell checkpoints markers as PD-L1 expression and tumour mutational burden.
Biomarkers were measured in blood in both cohorts. See bioanalytical reports included in Appendix 16.4. Of note: not all included patients had blood samples for biomarkers as per an Amendment to study protocol.

Statistical methods:
Analysis Set:

- Included Set (IS): all included patients.
- Safety Set (SS): patients who received at least one dose of IMP.
- Full Analysis Set (FAS): included patients who took at least one dose of IMP.
- Response Evaluable Set (RES): all patients of the FAS having at least one baseline and one post-baseline tumour evaluation. In the cohort B of the expansion part, only patients with MSS were considered evaluable.
- Dose-Limiting Toxicity Evaluable Set (DLTES): patients from the SS who were evaluable for DLT.

Efficacy analysis:
Descriptive statistics were provided for the overall response rate (ORR). The survival functions of the time dependent parameters [duration of response, Progression-Free Survival (PFS), overall survival (OS)] were estimated via Kaplan-Meier curves.

Safety analysis:
During the dose-escalation pat, the occurrence of DLT during the first 2 cycles was provided at each dose level. Descriptive statistics were provided for AEs, ECG parameters, physical examination, vital signs and laboratory tests.

Pharmacokinetic analysis:
See PK report included in Appendix 16.4 of this clinical study report.

Interim analyses in expansion cohorts:
During the expansion part, 2 interim analyses were performed independently in each cohort (A and B) in order to stop early the cohort for futility or for efficacy. The stopping rules were based on a Bayesian 3-stage design.

SUMMARY - CONCLUSIONS

DOSE-ESCALATION PART (N = 24)

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Status		25 mg/m² BID S95005 + 85 mg/m²/day Oxaliplatin	30 mg/m² BID S95005 + 85 mg/m²/day Oxaliplatin	35 mg/m² BID S95005 + 65 mg/m²/day Oxaliplatin	35 mg/m² BID S95005 + 85 mg/m²/day Oxaliplatin	All
Included	**n**	**4**	**3**	**3**	**14**	**24**
Withdrawn of treatment[1] due to	**n (%)**	**4 (100)**	**3 (100)**	**3(100)**	**14 (100)**	**24 (100)**
Progressive disease	n (%)	3 (75.0)	3 (100)	3 (100)	12 (85.7)	21 (87.5)
Non-medical reason	n (%)	1 (25.0)	-	-	1 (7.1)	2 (8.3)
Adverse event	n (%)	-	-	-	1 (7.1)	1 (4.2)
Withdrawn of follow-up due to	n (%)	**2 (50.0)**	**2 (66.7)**	**2 (66.7)**	**4 (28.6)**	**10 (41.7)**
Death for following reason:	n (%)	2 (50.0)	2 (66.7)	2 (66.7)[2]	4 (28.6)	10 (41.7)[2]
Progressive disease	n*(%)	2 (100)	2 (100)	2 (100)	4 (100)	10 (100)

Percentages are based on n (or n = # death). [1] Patient was considered discontinued from the treatment when S95005 was discontinued. [2] including 1 patient who died within 30 days after last intake i.e. during the treatment period*

Analysis sets		25 mg/m² BID S95005 + 85 mg/m²/day Oxaliplatin	30 mg/m² BID S95005 + 85 mg/m²/day Oxaliplatin	35 mg/m² BID S95005 + 65 mg/m²/day Oxaliplatin	35 mg/m² BID S95005 + 85 mg/m²/day Oxaliplatin	All
Included Set	**n**	**4**	**3**	**3**	**14**	**24**
Full Analysis Set	n (%)	4 (100)	3 (100)	3 (100)	14 (100)	24 (100)
Response Evaluable Set	n (%)	4 (100)	3 (100)	3 (100)	13 (92.9)	23 (95.8)
Safety Set	**n**	**4**	**3**	**3**	**14**	**24**
DLT Evaluable Set	n (%)	3 (75.0)	3 (100)	3 (100)	13 (92.9)	22 (91.7)

FAS % of IS; RES % of FAS; DLTES % of SS

BASELINE CHARACTERISTICS

Most of patients (87.5%) withdrew from study treatment for progressive disease, 2 patients (8.3%) for non-medical reason and 1 patient (4.2%) for adverse event.

The median age of patients was 61.0 years, 70.8% were aged ≤ 65 years and 62.5% were male. All had an ECOG PS of 0 or 1. The tumour localisation was left colon (including rectum) in 68.4% of patients and right colon (including transverse) in 31.6% of patients. The median disease duration was 2.5 years and the time since diagnosis of first metastasis was ≥ 18 months in 60.0% of patients.

Most of patients (83.3%) were pre-treated with at least 2 anti-neoplastic regimens (median number of prior regimens = 3), 70.8% had received oxaliplatin whatever the intent and 37.5% for adjuvant or neo-adjuvant setting.

EXTENT OF EXPOSURE

The median number of treatment cycles was 5.5 and 25.0% of patients were given more than 9 cycles (max 47 cycles). The median treatment duration was 12.0 weeks for S95005 and 10.9 weeks for oxaliplatin. The global compliance was high with a mean relative dose intensity (RDI) of 86.4 ± 16.9% for S95005 and 92.4 ± 10.2% for oxaliplatin. One third of patients had at least one cycle delayed and 3 patients (12.5%) had one S95005 dose reduction. All patients had full dose of oxaliplatin administered and no interruption during oxaliplatin infusion was reported.

EFFICACY RESULTS

Overall, in the dose-escalation part (n = 24), the BORs were PR in 2 patients (8.3%), SD in 13 patients (54.2%), PD in 8 patients (33.3%) and non-evaluable (NE) in 1 patient (4.2%). At RD (n = 14), the BORs were PR in 2 patients (14.3%), SD in 6 patients (42.9%), PD in 5 patients (35.7%) and NE in 1 patient (7.1%). Of note, the RD obtained in the study was 35 mg/m² BID for S95005 in combination with 85 mg/m²/day of oxaliplatin (refer to the Safety conclusions section)

Overall, the ORR, DCR and CBR were 8.3%, 62.5% and 54.2%, respectively. At RD, these efficacy rates were 14.3% for ORR and 57.1% for both DCR and CBR.

For the 2 responders with PR, the duration of response was 4.0 months for one patient and 4.9 months for the other. The median duration of clinical benefit was 6.5 months (95%CI = [3.8; 11.6]) both in overall patients (n = 13) and at RD (n = 8).

The median PFS was 3.8 months (95%CI = [1.8 ; 6.5]) in overall patients and 4.4 months (95%CI = [1.8 ; 9.2]) at RD. The median OS was 30.5 months (95%CI = [6.9 ; 30.5]) in overall patients and could not be calculated at RD. The survival rate at 6 months was 83.3% in overall patients and 85.7% at RD.

SAFETY RESULTS

Dose Limiting Toxicities, Maximum Dose Tolerated and Recommended Dose

During the dose-escalation, 17 patients were treated with 14-day cycles of S95005 plus oxaliplatin in 4 dose-level cohorts. Among those, 15 patients were evaluable for DLT at the end of cycle 2. One patient experienced a DLT grade 3 febrile neutropenia at the maximal planned dose of both components S95005 35 mg/m^2 BID + oxaliplatin 85 mg/m^2. After onset of this DLT, 3 patients were treated at the same dose level and no other DLTs were reported. Consequently, the MTD was established at S95005 35 mg/m^2 BID + oxaliplatin 85 mg/m^2. An additional 7 patients were then enrolled to generate further safety data at the MTD. None of these patients reported toxicities that would meet the DLT criteria. The RD was therefore defined as S95005 35 mg/m^2 BID + oxaliplatin 85 mg/m^2.

Emergent adverse events

The main results of AEs in overall patients and those at RD during the dose-escalation part in the Safety Set are summarised in the Table hereafter.

Overall summary for adverse events in overall patients and at RD during the dose-escalation part

		35 mg/m^2 BID of S95005 + 85 mg/m^2/day of oxaliplatin (N = 14)	**ALL (N = 24)**
Patients having reported at least one:			
EAE	n (%)	14 (100)	24 (100)
Treatment-related* EAE	n (%)	14 (100)	23 (95.8)
Severe (grade ≥ 3) EAE	n (%)	10 (71.4)	14 (58.3)
EAE related to S95005	n (%)	5 (35.7)	7 (29.2)
Serious AE (including death)	n (%)	5 (35.7)	9 (37.5)
Serious EAE (including death)	n (%)	5 (35.7)	9 (37.5)
EAE related to S95005	n (%)	3 (21.4)	4 (16.7)
EAE leading to S95005 withdrawal	n (%)	1 (7.1)	5 (20.8)
Severe EAE	n (%)	1 (7.1)	4 (16.7)
Serious EAE	n (%)	1 (7.1)	4 (16.7)
EAE related to S95005	n (%)	1 (7.1)	1 (7.1)
Severe EAE related to S95005	n (%)	1 (7.1)	1 (7.1)
Serious EAE related to S95005	n (%)	1 (7.1)	1 (4.2)
Patients included in dose-escalation who died during the study	n (%)	4 (28.6)	10 (41.7)
During treatment period	n (%)	-	1 (4.2)
During the follow-up period	n (%)	4 (28.6)	9 (37.5)

**related to S95005 and/or oxaliplatin*

All patients reported at least one EAE. The ***most frequently affected SOCs*** (≥ 50% of the patients) were Gastrointestinal disorders, Nervous system disorders (83.3% each), General disorders and administration site conditions (79.2%), Blood and lymphatic system disorders (62.5%) and Metabolism and nutrition disorders (50.0%).
The ***most common EAEs*** *(≥ 20% of patients)* were asthenia (70.8%), nausea (54.2%), diarrhoea (50.0%), decreased appetite, neutropenia (41.7% each), vomiting (37.5%), neuropathy peripheral (33.3%), anaemia (29.2%), peripheral sensory neuropathy, thrombocytopenia (25.0% each), and abdominal pain, constipation, dyspepsia and neutrophil count decreased (20.8% each).

Overall, 58.3% of patients experienced at least one ***severe (grade ≥ 3) EAE***. Severe EAEs reported in at least 2 patients were neutropenia (25.0%), malignant neoplasm progression (12.5%), blood loss anaemia, neuropathy peripheral, neurotoxicity, asthenia and hyponatraemia (8.3% each).
In patients at RD (n = 14), the distribution of EAEs and severe EAEs was similar to the one in all patients.

Almost all patients (95.8%) experienced at least one ***treatment-related EAE*** (*i.e.* related to S95005 and/or oxaliplatin), mainly grade 1 or 2. The most common treatment-related EAEs (≥ 20% of patients) were asthenia (62.5%), nausea (50.0%), diarrhoea (41.7%), neuropathy peripheral (33.3%), vomiting, decreased appetite and neutropenia (29.2% each), peripheral sensory neuropathy and thrombocytopenia (25.0% each), dyspepsia and neutrophil count decreased (20.8% each). Overall, 91.7% of patients reported at least one EAE related to S95005.

A total of 6 ***EAEs leading to S95005 withdrawal*** were reported in 5 patients (20.8%). These EAEs were malignant neoplasm progression (3 patients, 12.5%, including one fatal event), metastases to central nervous system (1 patient, 4.2%), nausea and vomiting (both events in the same patient). At RD, 2 EAEs (nausea and vomiting, both grade 3) leading to S95005 withdrawal were reported in 1 patient (7.1%). All were not related to S95005, except nausea and vomiting which were related to S95005.
Overall, 11 patients (45.8%) experienced at least one ***EAE leading to dose delay***. Among those events, the most common were related to hematologic toxicities i.e. neutropenia (25.0%), neutrophil count decreased (16.7%), thrombocytopenia (8.3%), anaemia, and blood loss anaemia (4.2%, each). At RD, the percentage of patients having at least one EAEs leading to dose delay was similar (42.9%) to the one in all patients. Overall, EAEs leading to IMP dose reduction were reported in 3 patients (12.5%): febrile neutropenia, asthenia and neutrophil count decreased in 1 patient each. None of patients experienced ***EAE leading to IMP dose reduction*** and dose delay. A total of 3 ***EAEs leading to IMP interruption*** were reported: nausea and vomiting, both in one patient, and asthenia in another patient.

Overall, 37.5% of patients had at least one ***serious EAE (SEAE)***. The SOCs affected by SEAEs were mainly Neoplasms benign, malignant and unspecified (5 patients, 20.8%), Gastrointestinal disorders (4 patients, 16.7%), Blood and lymphatic system disorders, and Infections and infestations (3 patients, 12.5%, each). SEAEs were sparsely distributed, each SEAE occurring in a single patient, except malignant neoplasm progression in 3 patients (12.5%) and blood loss anaemia in 2 patients (8.3%).
A total of 7 SEAEs related to S95005 were reported in 4 patients (16.7%): vomiting, nausea, febrile neutropenia, anaemia and thrombocytopenia (1 patient each). All those events except anaemia were reported at RD in 3 patients (21.4%).

Overall, 10 out of the 24 patients (41.7%) included in the dose-escalation died during the study: 1 patient (4.2%) during the treatment period due to a fatal EAE malignant neoplasm progression and 9 patients (37.5%) during the follow-up period from progressive disease. At RD, 4 out of the 14 patients (28.6%) died, all during the follow-up period.

Laboratory tests
For biochemical parameters, the most frequent emergent severe abnormal values (grade 3 or 4) were detected for high GGT in 7 patients [(29.2%), grade 3 (n = 6), grade 4 (n = 1)].
For haematological parameters, the most frequent emergent severe abnormal values were detected for low neutrophils (25.0% of overall patients), mostly of grade 3 (20.8%).

Other safety evaluation
No clinically relevant mean changes in body weight, BSA or vital signs were observed. ECOG PS was unchanged in 41.7% of patients. ECOG PS worsening from 0 or 1 at baseline to ≥ 2 at last visit on treatment was observed in 3 patients (12.5%).

EXPANSION PART (N = 54)

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Status		**Cohort A**	**Cohort B**	**All**
Included	n	37	17	54
Withdrawn of treatment[1] due to	n (%)	37 (100)	17 (100)	54 (100)
Progressive disease	n (%)	26 (70.3)	11 (64.7)	37 (68.5)
Adverse event	n (%)	7 (18.9)	1 (5.9)	8 (14.8)
Non-medical reason	n (%)	3 (8.1)	3 (17.7)	6 (11.1)
Physician decision	n (%)	1 (2.7)	2 (11.8)	3 (5.6)
Withdrawn of follow-up due to	n (%)	11 (29.7)	6 (35.3)	17 (31.5)
Death for following reasons:	n (%)	11 (29.7)	6 (35.3)	17 (31.5)
Progressive disease	n* (%)	9 (81.8)	5 (83.3)	14 (82.4)
Other	n* (%)	2 (18.2)	1 (16.7)	3 (17.7)

Percentages are based on n (or n = # death)*

[1] In the bevacizumab cohort (cohort A), a patient was considered discontinued from the treatment when S95005 was discontinued. In the nivolumab cohort (cohort B), a patient was considered discontinued from the treatment when S95005 and nivolumab were discontinued.

Analysis sets		**Cohort A**	**Cohort B**
Included Set	**n**	**37**	**17**
Full Analysis Set (FAS)	**n (%)**	**37 (100)**	**17 (100)**
Tumour FAS (N=11)	n (%)	-	11 (64.7)
Response Evaluable Set (RES)	n (%)	35 (94.6)	14 (82.4)
Tumour RES (N=8)	n (%)	-	8 (57.1)
Safety Set	**n (%)**	**37**	**17**

FAS % of IS; RES % of FAS; Tumour FAS % of FAS; Tumour RES % of RES

BASELINE CHARACTERISTICS AND EXTENT OF EXPOSURE

Cohort A

The median age of patients was 64.0 years, 51.4% were aged ≤ 65 years and 54.1% were male. All had an ECOG PS of 0 or 1. The tumour localisation was left colon in 67.6% of patients and right colon in 32.4% of patients. The median disease duration was 2.2 years and the time since diagnosis of first metastasis was ≥ 18 months in 35.1% of patients. Overall, 51.3% of patients were pre-treated with at least 2 anti-neoplastic regimens. Bevacizumab was taken previously in 56.8% of patients and oxaliplatin in 37.8% of patients.

The median number of treatment cycles was 12.0 and 62.2% of patients were given more than 9 cycles (max 46 cycles). The median treatment duration was 29.4 ± 21.2 weeks (median = 26.9) for S95005, 24.0 ± 19.4 weeks (median = 21.0) for oxaliplatin, and 28.7 ± 21.6 weeks (median = 26.7) for bevacizumab. The global compliance of each study drug was high. The mean RDI was 82.0 ± 10.1% for S95005, 82.5 ± 11.7% for oxaliplatin and 86.1 ± 9.6% for bevacizumab. Overall, 70.3% of patients had at least one cycle delayed; 18.9% of patients had at least one S95005 dose reduced. All patients had full dose administered of oxaliplatin, and bevacizumab. Oxaliplatin infusion was interrupted in 1 patient for vomiting and rash.

Cohort B

The median age of patients in Cohort B was 64.0 years, 64.7% were aged ≤ 65 years and 70.6% were male. All had an ECOG PS of 0 or 1. The tumour localisation was left colon in 82.4% and right colon in 17.6% of patients. The median disease duration was 1.8 years and the time since diagnosis of first metastasis was ≥ 18 months in 29.4% of patients.

Most of patients (76.5%) were pre-treated with at least 2 anti-neoplastic regimens. Bevacizumab was taken previously in 52.9% of patients and oxaliplatin in 35.3% of patients

The median number of treatment cycles was 8.0 and 41.2% of patients were given more than 9 cycles (max 56 cycles). The median treatment duration was 27.4 ± 29.2 weeks (median = 17.9) for S95005, 18.2 ± 11.6 weeks (median = 17.9) for oxaliplatin, and 27.4 ± 29.2 weeks (median = 17.9) for nivolumab. The global compliance of each study drug was high. The mean RDI was 86.9 ± 25.5% for S95005, 84.9 ± 26.4% for oxaliplatin and 89.2 ± 22.8% for nivolumab. Overall, 76.5% of patients had at least one cycle delayed; 41.2% of patients had one S95005 dose reduced. All patients had only full dose administered of oxaliplatin and nivolumab. Oxaliplatin infusion was interrupted in 1 patient for nausea.

EFFICACY RESULTS

Antitumoural activity

Cohort A

The BOR was CR in 1 patient (2.7%), PR in 5 patients (13.5%), SD in 25 patients (67.6%), PD in 4 patient (10.8%) and NE in 2 patients (5.4%). The ORR was 16.2% and both DCR and CBR were 83.8%. Among patients with CR and PR, the median duration of response was 17.3 months (95%CI = [4.3 ; 17.3]). The median duration of clinical benefit was 7.5 months (95%CI = [6.1 ; 10.8]). The median PFS was 6.9 months (95%CI = [5.5 ; 10.5]). The median OS was 15.1 months (95%CI = [11.7 ; not determined] and the survival rate at 6 months was 89.2%.

Cohort B

The BOR was PR in 2 patients (11.8%), SD in 9 patients (52.9%), PD in 5 patient (29.4%) and NE in 1 patient (5.9%). The ORR was 11.8% and both DCR and CBR were 64.7%. The duration of response for the 2 patients with PR was 3.7 and 26.5 months. The median duration of clinical benefit was 7.9 months (95%CI = [6.0 ; not reached]). The median PFS was 6.0 months (95%CI = 2.0 ; 8.0]). The median OS was 20.1 months (95%CI = [11.7 ; not determined] and the survival rate at 6 months was 81.6%.

Biomarkers in Cohort B

All patients from Cohort B had a tumour biopsy at baseline and 10 patients at Cycle 4 but samples from 9 and 6 respectively were evaluable for analysis.

At baseline, 2 patients had PD-L1 detected in 1% of tumour cells in one patient and 20% in the other. The mean density of intratumoral CD8+ TILs was 37.6 ± 39.6 cells/mm^2 (n = 9). Between baseline and cycle 4 on treatment, one patient showed an increase in percentage of PD-L1 tumour cells from 1% to 5% which was associated with clinical benefit. The mean change in CD8+ TILs density was 12.5 ± 95.8 cells/mm^2 (n = 4).

SAFETY RESULTS

Emergent adverse events

The main results of adverse events during the expansion part in the Safety Set are summarised in the Table hereafter.

Overall summary for adverse events in Cohort A and Cohort B during the expansion part

		Cohort A (N = 37)	Cohort B (N = 17)
Patients having reported at least one:			
EAE	n (%)	37 (100)	17 (100)
Treatment-related* EAE	n (%)	37 (100)	17 (100)
Severe (grade ≥ 3) EAE	n (%)	30 (81.1)	14 (82.4)
EAE related to S95005	n (%)	21 (56.8)	9 (52.9)
Serious AE (including death)	n (%)	13 (35.1)	10 (58.8)
Serious EAE (including death)	n (%)	12 (32.4)	9 (52.9)
EAE related to S95005	n (%)	5 (13.5)	3 (17.6)
EAE leading to S95005 withdrawal	n (%)	10 (27.0)	4 (23.5)
Severe EAE	n (%)	6 (16.2)	2 (11.8)
Serious EAE	n (%)	4 (10.8)	4 (23.5)
EAE related to S95005	n (%)	6 (16.2)	-
Severe EAE related to S95005	n (%)	3 (8.1)	-
Serious EAE related to S95005	n (%)	1 (2.7)	-
Patients included in expansion part who died during the study	n (%)	14 (37.8)	7 (41.2)
During treatment period	n (%)	3 (8.1)	1 (5.9)
During the follow-up period	n (%)	11 (29.7)	6 (35.3)

**related to S95005 and/or oxaliplatin and/or bevacizumab (Cohort A) and/or nivolumab (Cohort B)*

All patients reported at least one EAE in the two cohorts. ***The most frequently affected SOCs*** *(≥ 50% of the patients in either cohort)* were Gastrointestinal disorders and Nervous system disorders (78.4% in Cohort A and 94.1% in Cohort B for both), General disorders and administration site conditions, and Blood and lymphatic system disorders in both cohorts; and also, Investigations and, Musculoskeletal and connective tissue disorders in Cohort A.

The most common EAEs *(≥ 20% of patients in either cohort)* were:

- In Cohort A: nausea (59.5%), neutropenia (48.6%), diarrhoea (37.8%), vomiting (40.5%), peripheral sensory neuropathy (37.8%), fatigue, decreased appetite (35.1% each), asthenia (32.4%), neutrophil count decreased (32.4%), anaemia (27.0%), paraesthesia (24.3%), stomatitis and hypertension (24.3% each), platelet count decreased and pyrexia (21.6% each).

- In Cohort B: neutropenia (64.7%), diarrhoea (58.8%), nausea, vomiting and fatigue (47.1% each), asthenia and paraesthesia (41.2% each), decreased appetite (35.3%), anaemia, thrombocytopenia (29.4% each), peripheral sensory neuropathy and neuropathy peripheral (23.5% each).

Overall, 81.1% of patients experienced at least one ***severe (grade ≥ 3) EAE*** in Cohort A and 82.4% in Cohort B. The most common (≥ 10% of patients in either cohort) severe EAE were neutropenia (27.0%), hypertension (21.6%), neutrophil count decreased (13.5%) and malignant neoplasm progression (10.8%) in Cohort A; neutropenia (47.1%), fatigue (23.5%), anaemia (17.6%), thrombocytopenia, blood loss anaemia and diarrhoea (11.8% each) in Cohort B.

All patients experienced at least one ***treatment-related EAE***, mainly grade 1 or 2. The most common treatment-related EAEs (≥ 20% of patients in either cohort) were:

- Cohort A: nausea (54.1%), neutropenia (48.6%), diarrhoea and peripheral sensory neuropathy (37.8% each), vomiting (32.4%), fatigue and neutrophil count decreased (29.7% each), asthenia (27.0%), paraesthesia (24.3%), stomatitis, platelet count decreased and decreased appetite (21.6% each). In Cohort A, 97.3% of patients reported at least one EAE related to S95005.
- Cohort B: neutropenia (64.7%), nausea and fatigue (47.1% each), diarrhoea, vomiting and paraesthesia (41.2% each), asthenia and decreased appetite (35.3% each), thrombocytopenia (29.4%), peripheral sensory neuropathy and anaemia (23.5% each). In cohort B, all patients reported at least one EAE related to S95005.

In Cohort A, 12 ***EAEs leading to S95005 withdrawal*** were reported in 10 patients (27.0%), mostly malignant neoplasm progression (n = 4) and neutropenia (n = 3). Among those patients, 6 (16.2%) experienced EAEs related to S95005, mostly neutropenia (n =3).
In Cohort B, 4 EAEs leading to S95005 withdrawal were reported in 4 patients (23.5%): malignant neoplasm progression (n = 2), pancreatitis and muscular weakness (n = 1, each), all those events were not related to S95005.

In Cohort A, at least one ***EAE leading to dose delay*** was reported in 31 patients (83.8%), mostly neutropenia (37.8%) and neutrophil count decreased (29.7%); in Cohort B, those events were reported in 12 patients (70.6%), mostly neutropenia (52.9%). In Cohort A, at least one ***EAE leading to IMP dose reduction*** was reported in 6 patients (16.2%) with events sparsely distributed; in Cohort B, those events were reported in 4 patients (23.5%, neutropenia, febrile neutropenia, fatigue and asthenia in 1 patient each). In Cohort A, at least one ***EAE leading to IMP interruption*** was reported in 6 patients (16.2%); in Cohort B, those events were reported in 3 patients (17.6%).

In Cohort A, at least one ***serious EAE (SEAE)*** was reported in 12 patients (32.4%), mostly malignant neoplasm progression (4 patients, 10.8%). Among those patients, 5 (13.5%) experienced SEAEs related to S95005: lymphopenia, neutrophil count decreased, pancytopenia, diarrhoea, vomiting, stoma site haemorrhage and myocardial infarction (1 patient, each).
In Cohort B, at least one SEAE was reported in 9 patients (52.9%), mostly malignant neoplasm progression, anaemia and pulmonary embolism (2 patients, 11.8%, each). Among those patients, 3 patients (17.6%) experienced SEAEs related to S95005: anaemia, febrile neutropenia, thrombocytopenia, neutropenia, pneumonitis and pulmonary embolism (1 patient, each).

Overall, 21 out of the 54 patients (38.9%) included in the expansion died during the study: 14 patients (37.8%) in the Cohort A and 7 patients (41.2%) in the Cohort B. During the treatment period, 3 patients (8.1%) died in Cohort A (2 patients for disease progression and 1 patient for pneumonitis) and 1 patient (5.9%) died in Cohort B for disease progression. None of fatal EAEs on treatment were related to S95005. During the follow-up period, 11 patients (29.7%) died in Cohort A and 6 patients (35.3%) in Cohort B, mostly for progressive disease in the two cohorts.

Laboratory tests
For biochemical parameters, the most frequent emergent severe abnormal values (grade 3 or 4) were detected for high GGT both in Cohort A (5 patients, 13.5%) and in Cohort B (5 patients, 29.4%).
For haematological parameters, the most frequent emergent severe abnormal values were detected for low neutrophils (Cohort A 37.8%, Cohort B 47.1%), low WBC (Cohort A, 29.7%; Cohort B, 29.4%) and low lymphocytes (Cohort A, 24.3%; Cohort B 29.4%).

Other safety evaluation
No clinically relevant mean changes in body weight, BSA or vital signs were observed. ECOG PS was unchanged in 75.7% of patients in Cohort A and in 68.8% of patients in Cohort B. ECOG PS worsening from 0 or 1 at baseline to ≥ 2 at last visit on treatment was observed in 3 patients (8.1%) in Cohort A and 2 patients (12.5%) in Cohort B.

CONCLUSION

This study was an open-label, non-randomised, dose-escalation phase I study aimed to assess the safety, the MTD, and the RD of S95005 in combination with oxaliplatin on a 14-day cycle in patients with metastatic CRC previously treated by at least one line of standard chemotherapy. The dose-escalation was followed by an expansion part with the addition on day 1 of bevacizumab 5 mg/kg (Cohort A) or nivolumab 3 mg/kg (Cohort B) to the combination of S95005 with oxaliplatin at the RD.

A total of 78 patients were included in the study: 24 in the dose-escalation part and 54 in the expansion part (37 patients in Cohort A, 17 patients in Cohort B).

During dose-escalation, one dose-limiting toxicity of grade 3 febrile neutropenia was observed at the maximal planned dose of both components *i.e.* 35 mg/m2 of S95005 twice daily, days 1-5, and 85 mg/m2 of oxaliplatin day 1, which was established as the MTD and subsequently the RD. In overall patients, the most common adverse events reported with the combination were those expected with each component as monotherapy i.e. gastrointestinal and hematologic relative events with S95005 and neuropathy relative events with oxaliplatin. The most common treatment-related adverse events (≥ 20% of patients) were asthenia, nausea, diarrhoea, neuropathy peripheral, vomiting, decreased appetite, neutropenia, peripheral sensory neuropathy, thrombocytopenia, dyspepsia and neutrophil count decreased. Among treatment-related adverse events, those of grade 3 were 7.5% and those of grade 4 were 1.4%. Best overall responses at the RD (n = 14) were partial response in 2 patients (14.3%), stable disease in 6 patients (42.9%), progressive disease in 5 patients (35.7%) and non-evaluable in 1 patient (7.1%) corresponding to an objective response rate of 14.3%.

During the expansion part, recruitment in Cohort B was stopped early due to low response rate observed at interim efficacy analysis. In both cohorts, the most common adverse events were relative to gastrointestinal, neuropathy, general disorders and hematologic disorders. The most common treatment-related adverse events (≥ 20% of patients) were nausea, neutropenia, diarrhoea, peripheral sensory neuropathy and vomiting in Cohort A; neutropenia, nausea, fatigue, diarrhoea, vomiting, paraesthesia, asthenia and decreased appetite in Cohort B. Among treatment-related adverse events, those of grade 3 were 12.3% in Cohort A and 14.4% in Cohort B; those of grade 4 were 0.8% and 1.5%, respectively. The objective response rate was 16.2% in Cohort A and 11.8% in Cohort B; respective values for median progression-free survival were 6.9 and 6.0 months.

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