2. SYNOPSIS

Name of Sponsor: Institut de Recherches Internationales Servier (I.R.I.S)		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Futuximab/modotuximab (S95026 or Sym 004) Trifluridine and tipiracil hydrochloride (S95005)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: A randomised, open-label, multi-centre, two-arm Phase 3 study comparing futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil single agent with a Safety Lead-In part in participants with KRAS/NRAS and BRAF wild type metastatic colorectal cancer previously treated with standard treatment and anti-EGFR therapy (COLSTAR).
Protocol No.: CL3-95026-001
EudraCT No.: 2021-003151-41
ClinicalTrials.gov: NCT05223673
Investigational New Drug No: 105953
The description of the study protocol given hereafter includes the modifications of the 2 substantial amendments to the protocol.

International coordinator
[redacted]

Study countries:
Five countries included 7 participants: Belgium and Hungary (2 participants each), Finland, Japan and United States (US) of America (1 participant each).

Publication (reference):
Not applicable

Studied period: Initiation date: 21 April 2022 (first visit of first participant) Completion date: 21 June 2023 (last visit of last participant)	**Phase of development of the study:** Phase 3 with Safety Lead-In part

Objectives for Lead-in part:
Primary objective

- To assess safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Secondary objectives

- To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil per investigator assessment using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in terms of:
  - Objective Response Rate (ORR).
  - Best Overall Response (BOR).
  - Disease Control Rate (DCR).
  - Progression Free Survival.
- To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil in terms of Overall Survival.
- To characterise the pharmacokinetic (PK) profile of futuximab/modotuximab, trifluridine and tipiracil in the combination of futuximab/modotuximab with trifluridine/tipiracil.
- To evaluate the immunogenicity of futuximab/modotuximab (*i.e.,* occurrence of anti-drug antibody [ADA]).

Exploratory objective

- To explore biomarkers as potential predictors of response and to track the emergence of resistance.

Methodology/Study design:
This was a Phase 3 study with a Safety Lead-in part:

- The Safety Lead-in was an international, open-label, single-arm, non-randomised part, with the aim to evaluate the safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil in participants previously treated by chemotherapy and by anti- Epidermal Growth Factor Receptor (EGFR) monoclonal antibody (mAb) therapy for ≥ 16 weeks, with KRAS/NRAS and BRAF Wild Type (WT) metastatic colorectal cancer (mCRC).
- The Randomised part was an international, open-label, randomised, multi-centre, parallel-group, 2-arm part.

During the Lead-in part, the sponsor decided to discontinue the study due to strategic reasons. This decision was not a safety measure. The Randomised part was not started due to study discontinuation.

In this context, an abbreviated clinical study report (CSR) was presented. This study was performed in strict accordance with Good Clinical Practice (GCP).

Number of participants in Safety Lead-in part :
Planned: approximately 25 participants with a minimum of 3 Japanese participants.
Included: 7 participants including 1 Japanese participant.

Diagnosis and main criteria for screening/inclusion:

- Male or female participant ≥ 18 years old
- Participants must have histologically or cytologically confirmed adenocarcinoma of mCRC (all other histological types were excluded), not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumour.
- Based on circulating tumour (ct) DNA screening blood test analysis participants should be:
  - Without RAS (KRAS and NRAS) mutations in any of the following codons:
    - Exon 2: codon 12, 13.
    - Exon 3: codon 59, 61.
    - Exon 4: codon 117, 146.
  - Without BRAF V600E mutation.
- Participants must have measurable or non-measurable lesion according to RECIST v1.1.
- Participants must have received at least 2 prior regimens of standard chemotherapy for mCRC and had demonstrated progressive disease or intolerance to their last regimen.

The following characteristics applied:

- Prior standard chemotherapy must not have included trifluridine/tipiracil but must have included all of the following agents approved and available in each country:
  - Fluoropyrimidines, irinotecan and oxaliplatin.
  - At least one anti-Vascular Endothelial Growth Factor (VEGF) pathway inhibitor (bevacizumab and/or aflibercept and/or ramucirumab and/or regorafenib).
  - At least one anti-EGFR mAb (cetuximab or panitumumab).
  - Participants with known Microsatellite Instability High (MSI-H)/deficient Mismatch Repair (dMMR) tumours were eligible if they have received previous treatment with immune checkpoint inhibitors according to approved indication.
- Participants must have progressed during or within 6 months of the last administration of the last standard chemotherapy regimen. Participants who had withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease were eligible to enter the study.
- Participants who received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy were permitted to count the adjuvant/neoadjuvant therapy as one regimen of chemotherapy.

- Participants should have received previous treatment with commercially available anti-EGFR mAbs for ≥ 16 weeks.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (or equivalent Karnofsky Performance Status [PS] of 70% to 100%).
- Adequate haematological, renal and hepatic functions based on blood laboratory values. Serum potassium, serum phosphates, serum magnesium within normal limits with or without supplementation.

Test drug: futuximab/modotuximab + trifluridine/tipiracil

Futuximab/modotuximab

Futuximab/modotuximab was administered at a dose 9 mg/kg on Cycle 1 Day 1 (C1D1) (loading dose) and then at a 6 mg/kg weekly beginning on C1D8 (maintenance doses) for all subsequent administrations, by intravenous (IV) infusion, after trifluridine/tipiracil intake. The first infusion on C1D1 (9 mg/kg in 500 mL) had to be administered over 1 hour. The maximum rate of infusion of 500 mL/hour should not be exceeded throughout the administration. Subsequent infusions (6 mg/kg in 250 mL) could be delivered over 30 minutes, maintaining the maximum infusion rate of 500 mL/hour. Premedication for prophylaxis of infusion related reactions was mandatory prior to each dose of futuximab/modotuximab.

Trifluridine/tipiracil

Trifluridine/tipiracil was administered, before futuximab/modotuximab administration, at a dose 35 mg/m²/dose, orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 14 days (2 weeks), followed by a 14-day (2 weeks) rest.
This treatment cycle was repeated every 28-days (4 weeks).

Comparator:
Not applicable for Safety Lead-in part.

Duration of treatment:
Treatment period: participants were treated until they met a discontinuation criterion.
Follow-up period: after the withdrawal visit, participants were followed every 8 weeks:

- For survival status until the end of the study.
- For tumour assessment (if the patient was withdrawn from the study for another reason than radiologic disease progression).

Criteria for evaluation:
Efficacy measurements:
Tumour evaluations were performed based on investigator assessment as per RECIST v1.1 at baseline and then every 8 weeks until radiologic disease progression regardless of initiation of new anticancer therapy.

Safety measurements:
Standard safety monitoring was performed including physical examination, vital signs, ECOG PS, Electrocardiogram (ECG), adverse events (AEs), dermatologic examination and clinical laboratory evaluation.

Pharmacokinetic measurements: not performed.

Statistical methods:
Analysis Set:
Screened set: all participants screened.
Safety Set (SS): All participants having taken at least one dose of Investigational Medicinal Products (IMPs). SS was used in all analyses.
Dose-Limiting Toxicity (DLT) Evaluable Set (DLTES): all participants in the SS who were evaluable for DLTs.

Efficacy analysis:
In the context of an abbreviated CSR, only Best Overall Response (BOR) analysis was performed.

Patient disposition, baseline characteristics, treatments and safety analyses: Descriptive statistics were provided in the SS unless otherwise specified.

SUMMARY - CONCLUSIONS

A total of 13 participants were screened. Of them, 7 participants were included, and all received the study treatment (Safety Set: N = 7).

BASELINE CHARACTERISTICS

The mean ± standard deviation (SD) age of participants was 67.3 ± 3.7 years (range: 61 - 73 years). There were 5 (71.4%) male participants and 2 (28.6%) female participants.
At baseline, all participants had unresectable metastatic adenocarcinoma of colorectal cancer (CRC). The primary tumour localisation was left colon for all participants. The mean ± SD number of metastatic organ sites was 2.4 ± 1.3 with mostly affected organ sites of lung (6 participants, 85.7%) and liver (5 participants, 71.4%).
The mean disease duration was 4.0 years and mean time from first metastasis diagnosis to inclusion was 37.8 ± 22.6 months. Participants received a mean of 4.1 ± 2.5 (range: 2 to 9) prior regimens of anticancer treatment for metastatic intent. All participants received prior fluoropyrimidine, irinotecan, anti-VEGF mAb and anti-EGFR mAb and 6 (84.7%) participants received oxaliplatin for metastatic intent. The mean duration of prior anti-EGFR mAb treatment was 16.5 ±14.6 months (range: 4 - 46 months).
At baseline, ECOG PS was rated 0 in 5 (71.4%) participants and 1 in 2 (28.6%) participants.

EXTENT OF EXPOSURE

The mean ± SD trifluridine/tipiracil treatment duration was 3.6 ± 3.0 months (range: 0.9 - 10.1 months) and the mean ± SD number of cycles was 3.6 ± 2.6 (range: 1 - 9). The mean ± SD number of futuximab/modotuximab infusions was 12.6 ± 10.0 (range: 4 - 34).

EFFICACY RESULTS

In the context of an abbreviated CSR, only BOR analysis was performed. Out of the 7 participants, the BOR was stable disease in 4 (57.1%) participants, progressive disease in 2 (28.6%) participants and non-evaluable in 1 (14.3%) participant.

SAFETY RESULTS

No DLT was reported.

Treatment-emergent AEs (TEAEs) reported in ≥ 2 participants were dermatitis acneiform (6 participants, 85.7%), neutropenia, hypomagnesaemia, dry skin (5 participants, 71.4% each), fatigue, infusion related reaction (4 participants, 57.1% each), nausea, decreased appetite (3 participants, 42.9% each) and, constipation, oedema peripheral, dysgeusia, hypocalcaemia, erythema, pruritus (2 participants, 28.6% each).

All participants experienced at least one ***severe TEAE***. The following severe TEAEs occurred in 2 (28.6%) participants: neutropenia, hypomagnesaemia and dermatitis acneiform. All other severe TEAEs occurred in 1 (14.3%) participant each: vertigo, fatigue, cholecystitis acute, jaundice, pneumonia bacterial, sepsis, confusional state, dyspnoea, hyperventilation and rash maculo-papular (all Grade 3, except sepsis which was fatal).

All participants experienced at least one ***treatment-related TEAE***. Treatment-related TEAEs reported in ≥ 2 participants were dermatitis acneiform (6 participants, 85.7%), neutropenia, hypomagnesaemia, dry skin (5 participants, 71.4% each), infusion related reaction (4 participants, 57.1%), nausea, fatigue, decreased appetite (3 participants, 42.9% each) and, dysgeusia, hypocalcaemia, erythema, pruritus (2 participants, 28.6% each). Severe treatment-related TEAEs were reported in 5 (71.4%) participants as following: neutropenia, hypomagnesaemia, dermatitis acneiform (2 participants, 28.6% each), fatigue and rash maculo-papular (1 participant, 14.3% each).

Overall, 1 (14.3%) participant experienced one ***TEAE leading to trifluridine/tipiracil withdrawal*** (fatigue) which was severe, non-serious and treatment-related. There was also 1 (14.3%) participant experiencing one ***TEAE leading to futuximab/modotuximab withdrawal*** (rash maculo-papular) which was severe, non-serious and treatment-related (related to futuximab/modotuximab only).

Overall, 3 (42.9%) participants experienced at least one ***serious TEAE***. Each serious TEAE (as preferred term [PT]) occurred in 1 (14.3) participant as following: vertigo, cholecystitis acute, jaundice, pneumonia bacterial, sepsis, blood creatinine increased and hyperventilation (none were treatment-related).

One participant died during the study. ***Death*** occurred as fatal outcome of treatment-emergent sepsis (not treatment-related).

CONCLUSION

This was a Phase 3 study with a Safety Lead-in part and a Randomised part. The Safety Lead-in was an international, open-label, single-arm part, with the aim to evaluate the safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil in participants previously treated by chemotherapy and by anti-EGFR monoclonal antibody therapy for ≥ 16 weeks, with KRAS/NRAS and BRAF WT metastatic colorectal cancer. During the Safety Lead-in part, the sponsor decided to discontinue the study for strategic reasons. This decision was not a safety measure. The Randomised part was not started.

Overall, 7 participants received weekly intravenous infusions of futuximab/modotuximab (loading dose 9 mg/kg then 6 mg/kg) in combination with trifluridine/tipiracil over 28-day cycles of treatment.

No DLTs were reported.

TEAEs reported in participants treated with the combination futuximab/modotuximab plus trifluridine/tipiracil were consistent with the known safety profile of each of the 2 test drugs. Treatment-related TEAEs were mainly dermatitis acneiform (6 participants), neutropenia, hypomagnesaemia, dry skin (5 participants each), infusion related reaction (4 participants each), and nausea, fatigue, decreased appetite (3 participants each). Severe treatment-related TEAEs were neutropenia, hypomagnesaemia, dermatitis acneiform (2 participants each), fatigue and rash maculo-papular (1 participant, each). Overall, 3 participants experienced at least one serious TEAE, and none of those events were treatment-related.

Date of the report: 04 December 2023

Version of the report: Final Version