2. SYNOPSIS

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Test drug **Name of Finished Product:** Lonsurf® **Name of Active Ingredient:** S95005 (TAS-102): Trifluridine (FTD) and tipiracil hydrochloride (TPI)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: An open-label, randomised, non-comparative phase 2 study evaluating S95005 (TAS-102) plus bevacizumab and capecitabine plus bevacizumab in patients with previously untreated metastatic COlorectal cancer who are non-eligible for intensive therapy (TASCO1 study).
Protocol No.: CL2-95005-002
EudraCT No.: 2015-004544-18
Since the release of the primary clinical study report (CSR), there was 1 substantial amendment to the protocol to update the end of study as the last patient withdrawal visit.

Main coordinator

[redacted]

Study countries:
Twelve countries included 153 patients: Australia (1 patient), Belgium (5 patients), Brazil (4 patients), Denmark (7 patients), France (7 patients), Germany (6 patients), Italy (9 patients), Netherlands (28 patients), Poland (21 patients), Russia (22 patients), Spain (20 patients) and United Kingdom (23 patients).

Publication (reference):
E.Van Cutsem, *et al.*, Trifluridine/tipiracil plus bevacizumab in patients with untreated metastatic colorectal cancer ineligible for intensive therapy: the randomized TASCO1 study. Ann Oncol. 2020 Sep;31(9):1160-1168.

Studied period:	**Phase of development of the study:**
Initiation date: 29 April 2016 (first visit first patient) Cut-off for primary analysis: 15 January 2018 Completion date: 01 September 2020 (last patient last withdrawal visit)	Phase II

Objectives:
Primary
Progression-free survival (PFS) based on Investigator assessment of radiologic images.
Secondary: Overall response rate (ORR)**,** Duration of response (DR)**,** Disease control rate (DCR)**,** Overall survival (OS)**,** Safety and tolerability**,** Quality of life (QoL).
Exploratory
Evaluate the biomarkers potentially predictive of response and resistance to S95005 given in combination using blood samples and archived tumour biopsy (if available).

Methodology:
This was a multinational, open-label, two-arm, randomised phase 2 study evaluating S95005 + bevacizumab and capecitabine + bevacizumab in the first-line treatment of patients with unresectable metastatic colorectal cancer (mCRC) who are non-eligible for intensive therapy.
Patients were randomised in a (1:1) ratio with the minimisation procedure proposed by Pocock and Simon. The stratification factors were RAS status (wild-type, mutant type), Eastern Cooperative Oncology Group (ECOG) performance status (0 *vs* 1 *vs* 2) and country.

The primary CSR of 24 September 2018 presented the results of the primary PFS analysis once the 100th PFS event has been observed as well as other clinical data. The present final CSR describes the results based on full data up to the end of study, including overall survival which was not enough mature at the primary analysis.

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

Number of patients:
Planned: 150 patients in total (75 patients per group)
Included: 153 patients (77 patients in the S95005 + bevacizumab group and 76 patients in the capecitabine + bevacizumab group).

Diagnosis and main criteria for inclusion:
Male or female participants aged ≥ 18 years old, having definitive histological or cytological confirmation of adenocarcinoma of the colon or rectum, RAS status determined on tumour biopsy (mutant or wild-type), with at least one measurable metastatic lesion according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria (v1.1), unresectable metastatic disease diagnosed within 6 months prior to the first study drug intake, ECOG performance status ≤ 2 and adequate hepatic, renal, and haematological functions.
Patients should not have received previous systemic anticancer therapy for unresectable mCRC, however previous adjuvant (or neoadjuvant for patients with rectal cancer) chemotherapy was allowed only if treatment had been completed more than 6 months before start of study treatment. Patients could not have been candidates for combination chemotherapy with irinotecan or oxaliplatin and for curative resection of metastatic lesions, according to the investigator's judgment.

Test drug: S95005 + bevacizumab
S95005 (35 mg/m²/dose) was administered orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; with bevacizumab [5 mg/kg, intravenously (IV)] administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.

Reference product: Capecitabine + bevacizumab
Capecitabine (1250 mg/m²) was administered orally BID on Days 1–14 of each cycle, with bevacizumab (7.5 mg/kg, IV) administered on Day 1 of each cycle. This treatment cycle was repeated every 3 weeks.
Note: according to local clinical practice the starting dose of capecitabine could be reduced to 1000 mg/m².

Duration of treatment:
Screening period and inclusion: up to 28 days prior to inclusion visit/randomisation.
Treatment period: each patient had to complete at least one 28-day cycle of combination of S95005+ bevacizumab or at least 21-day cycle of combination of capecitabine + bevacizumab except in case of safety concerns. Patients were treated with the assigned combined regimen until they met a discontinuation criterion.
Follow-up period: after end of the treatment until the end of the study; patients who discontinued study treatment for reasons other than radiologic disease progression (*e.g.*, intolerable side effects) were followed for tumour response until radiologic disease progression or death, or initiation of new anticancer therapy (whichever occurred first); patients who discontinued study treatment for radiologic progression disease were followed for survival until the end of the study.

Criteria for evaluation:
Efficacy measurements:
Tumour assessments were analysed using RECIST v1.1 every 8 weeks until progression, death or initiation of a new anticancer treatment (whichever occurred first).

Quality of Life was assessed every 12 weeks using 2 questionnaires ([The European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ)-C30 and QLQ-CR29].

Safety measurements:
Standard safety monitoring was performed and adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Biomarkers measurements:

- Blood samples: genomic analysis including KRAS, NRAS and BRAF mutation on circulating tumour DNA and proteomic analysis including thymidine phosphorylase on blood circulating proteins.
- Intratumoural biomarkers (if available): genomic and proteomic expression including microsatellite instability.

Statistical methods:

Analysis Set:

The Full Analysis Set (FAS) for the main efficacy analysis consisted of all randomised patients who have taken at least one dose of Investigational Medicinal Product (IMP). See the primary CSR for the description of all analysis sets.

Efficacy analysis:

Primary endpoint:

Primary analysis of the PFS: in the FAS, the Hazard Ratio (HR) and the corresponding 2-sided 80% and 2-sided 95% CIs for S95005 + bevacizumab *vs* capecitabine + bevacizumab were estimated using a Cox proportional hazard model adjusting for the stratification factor based on IWRS data (except country due to the large number of countries in the study). PFS for each arm was summarized using Kaplan-Meier curves and further characterized in terms of the median and progression-free survival probabilities at 2, 4, 6, and 12 months along with the corresponding 2-sided 80% and 2-sided 95% CI for the estimates (Brookmeyer and Crowley CI for median and Kalbfleisch and Prentice CI for survival probabilities).

Secondary analyses of the PFS: the primary analysis was repeated in the PPS and another sensitivity analysis taking into account further anti-cancer therapy as an event was carried out both in the FAS and the PPS, the analysed parameter was noted as PFSs1. In addition, a sensitivity analysis of PFS taking into account clinical progression (*i.e.* not only based on radiological assessment) was performed in the FAS and was noted as PFSs2.

Secondary endpoints:

Analysis of OS used the same population and analytical methods as described for PFS in the primary analysis.
Analysis of DR used similar analytical methods but based on the tumour response (TR) population.
DCR and ORR in the TR population was evaluated in each arm with their 2-sided 95% Clopper-Pearson CIs.

Study patients, Quality of Life and Safety analysis: descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS

Reason for treatment withdrawal		S95005 + bevacizumab (N = 77)	Capecitabine + bevacizumab (N = 76)	All (N = 153)
Included*	**n**	**77**	**76**	**153**
Treatment withdrawal due to	**n (%)**	**77 (100)**	**76 (100)**	**153 (100)**
Progressive disease	n (%)	47 (61.0)	50 (65.8)	97 (63.4)
Adverse event	n (%)	18 (23.4)	17 (22.4)	35 (22.9)
Non-medical reason	n (%)	8 (10.4)	3 (3.9)	11 (7.2)
Physician decision	n (%)	3 (3.9)	6 (7.9)	9 (5.9)
Protocol violation	n (%)	1 (1.3)	-	1 (0.7)

** one patient was randomised but not included and did not receive any study drug*
% expressed as percentage of the included patients by group

BASELINE CHARACTERISTICS

See the primary CSR, as the final analysis of the baseline characteristics showed same results than those obtained at the primary analysis.

EXTENT OF EXPOSURE

Updated extent of exposure was as follows. The mean (median) number of cycles was 10.2 ± 8.4 (8.0) in the S95005 + bevacizumab group and 11.4 ± 10.8 (9.0) in the capecitabine + bevacizumab group. The mean (median) treatment duration of study drug was higher in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 46.4 ± 40.6 (34.6) weeks *vs* 36.0 ± 35.0 (25.6) weeks.

Most of patients had at least one cycle delayed with a slightly higher frequency in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 79.2% vs 75.0% (median number of cycles delayed: 4.0 *vs* 1.0, respectively). The percentage of patients who had at least one cycle with dose reduction was lower in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 41.6% *vs* 52.6%.

The mean relative dose intensity of S95005 and capecitabine were unchanged as compared to the primary analysis (80.6 ± 15.3% vs 84.5 ± 16.6%, respectively).

EFFICACY RESULTS

Of note: the differences between the treatment groups presented hereafter are descriptive and not aiming to claim for any superiority of one treatment group above another.

- **Primary efficacy endpoint**

At final end-of-study analysis, among the first 100 PFS events observed, 49 were in the S95005 + bevacizumab group (63.6% of patients) and 51 in the capecitabine + bevacizumab group (67.1% of patients). The median PFS was unchanged as showed in the primary analysis: 9.2 months in the S95005 + bevacizumab group and 7.8 months in the capecitabine + bevacizumab group. The HR between the two treatment groups was 0.74, 95%CI = [0.50, 1.10], 80%CI = [0.57, 0.96].

The probability of progression-free survival was greater at each time-point evaluated (2, 4, 6, 12 months) in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group, and was 0.4 and 0.3, respectively, at latest time-point *i.e.* at 1 year.

- **Secondary efficacy endpoints**

Overall response rate, disease control rate, duration of response

At final end-of-study analysis, ORR was quite unchanged in comparison with results obtained at the primary analysis: 35.1% in the S95005 + bevacizumab group and 31.6% in the capecitabine + bevacizumab group. DCR was unchanged: 85.7% and 77.6%, respectively.

One patient (1.3%) had a confirmed CR in the capecitabine + bevacizumab group. The frequency of patients having confirmed PR was 35.1% in the S95005 + bevacizumab group and 30.3% in the capecitabine + bevacizumab group, for SD: 50.6% and 46.0%, respectively, and for PD: 5.2% and 15.8%, respectively.

The median DR was 7.9 months and 9.7 months, respectively.

Overall survival

At final end-of-study analysis, the median OS was 22.3 months in the S95005 + bevacizumab group and 17.7 months in the capecitabine + bevacizumab group. The HR between the two treatment groups was 0.78, with 95%CI = [0.55, 1.10], 80%CI = [0.62, 0.98]. The probability of overall survival was greater at each time-point evaluated (2, 4, 6, 12, 18 and 24 months) in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group, and was 0.4 and 0.3, respectively, at latest timepoint *i.e.* at 2 years.

SAFETY RESULTS

- **Emergent adverse events**

The main results of AEs in the Safety Set are summarised in the Table hereafter.

		S95005 + bevacizumab (N = 77)	**Capecitabine + bevacizumab (N = 76)**
Patients having reported at least one:			
EAE	n (%)	77 (100)	74 (97.4)
Treatment-related EAE	n (%)	75 (97.4)	68 (89.5)
Severe (Grade ≥ 3) EAE	n (%)	68 (88.3)	54 (71.1)
Treatment-related	n (%)	60 (77.9)	33 (43.4)
Serious EAE (including death)	n (%)	51 (66.2)	45 (59.2)
Treatment-related	n (%)	28 (36.4)	18 (23.7)
EAE leading to treatment withdrawal	n (%)	33 (42.9)	32 (42.1)
Severe EAE	n (%)	24 (31.2)	21 (27.6)
Serious EAE	n (%)	23 (29.9)	18 (23.7)
Treatment-related EAE	n (%)	15 (19.5)	12 (15.8)
Treatment-related severe EAE	n (%)	10 (13.0)	7 (9.2)
Treatment-related serious EAE	n (%)	10 (13.0)	4 (5.3)
Patients who died during the study	n (%)	66 (85.7)	66 (86.8)
During treatment period	n (%)	4 (5.2)	9 (11.8)
During the follow-up period	n (%)	62 (80.5)	57 (75.0)

Treatment-related = related to study drug (S95005/capecitabine) and/or bevacizumab

The ***most frequently affected SOCs*** were Gastrointestinal disorders and Blood and lymphatic system disorders, both with higher frequency in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 85.7% *vs* 68.4%, and 72.7% vs 21.1%, respectively in the two SOCs. The other commonly affected SOCs were General disorders and administration site conditions (64.9% *vs* 57.9%), Skin and subcutaneous tissue disorders with a lower frequency in the S95005 + bevacizumab group (28.6% *vs* 61.8%), and, with a higher frequency in the S95005 + bevacizumab group, Investigations (59.7% *vs* 38.2%) and Infections and infestations (57.1% *vs* 40.8%).

The ***most commonly reported EAEs*** (≥ 20% of patients) in the S95005 + bevacizumab group were neutropenia (54.5% *vs* 7.9% in the capecitabine + bevacizumab group), diarrhoea (54.5% vs 44.7%), nausea (49.4% *vs* 18.4%), fatigue (39.0% *vs* 30.3%), decreased appetite (37.7% *vs* 19.7%), anaemia (33.8% *vs* 6.6%), vomiting (29.9% *vs* 13.2%), malignant neoplasm progression (26.0% vs 26.3%), neutrophil count decreased (24.7% *vs* 2.6%) and alopecia (23.4% *vs* none). All those EAEs were more frequent in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group, except for malignant neoplasm progression.
In the capecitabine + bevacizumab group, the most frequent EAEs were diarrhoea, fatigue and malignant neoplasm progression as described above, palmar-plantar syndrome (hand-foot syndrome) with lower frequency in the S95005 + bevacizumab group (3.9% *vs* 52.6% in the capecitabine + bevacizumab group), asthenia (18.2% *vs* 23.7%) and stomatitis (18.2% *vs* 21.1%). Febrile neutropenia was reported with similar frequency in the two treatment groups (5.2% *vs* 3.9%)

Patients affected by at least one ***severe EAE*** (Grade ≥ 3) were more frequent in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (88.3% *vs* 71.1%).
In the S95005 + bevacizumab group, the most frequent (> 10%) severe EAEs were reported with higher frequency in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group, except for malignant neoplasm progression: neutropenia (46.8% *vs* 5.3%), anaemia (13.0% *vs* none), neutrophil count decreased (19.5% *vs* 1.3%), white blood cell (WBC) count decreased (11.7% *vs* 2.6%), malignant neoplasm progression (16.9% *vs* 19.7%) and hypertension (13.0% *vs* 3.9%).
In the S95005 + bevacizumab group, neutropenia was Grade 3 in 20.8% of patients and Grade 4 in 26.0%, and neutrophil count decreased were Grade 3 in 13.0% and Grade 4 in 6.5%. Febrile neutropenia was Grade 3 in 2 patients and Grade 4 in 2 patients, and all recovered.
In the capecitabine + bevacizumab group, the most frequently severe EAEs were malignant neoplasm progression (see above) and palmar-plantar syndrome (none in the S95005 + bevacizumab group *vs* 11.8%, all Grade 3). Febrile neutropenia was Grade 3 in 2 patients, Grade 4 in 1 patient, and all recovered.

Most of the patients had at least one ***treatment-related EAE*** (to S95005/capecitabine and/or bevacizumab) with a higher frequency reported in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 97.4% *vs* 89.5%.
In the S95005 + bevacizumab group, the most common (> 20%) treatment-related EAEs, all with a higher frequency than in the capecitabine + bevacizumab group, were neutropenia (54.5% *vs* 5.3%), anaemia (27.3% *vs* 5.3%), neutrophil count decreased (23.5% *vs* 2.6%), diarrhoea (42.9% *vs* 36.8%), nausea (40.3% *vs* 4.5%), vomiting (22.1% *vs* 9.2%), fatigue (32.5% *vs* 25.0%), decreased appetite (29.9% *vs* 17.1%) and alopecia (20.8% *vs* none).
In the capecitabine + bevacizumab group, the most common treatment-related EAEs were palmar-plantar syndrome (51.3%) with a higher frequency than in the S95005 + bevacizumab group (3.9%), diarrhoea and fatigue as described above, and stomatitis (18.2% in the S95005 + bevacizumab group *vs* 21.1% in the capecitabine + bevacizumab group).
Severe treatment-related EAEs were reported with a higher frequency in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (77.9% *vs* 43.4%). This higher frequency in the S95005 + bevacizumab group was reported for neutropenia (46.8% vs 2.6%), neutrophil count decreased (18.2% *vs* 1.3%), WBC count decreased (11.7% *vs* 1.3%), anaemia (10.4% *vs* none), hypertension (6.5% *vs* 3.9%) and febrile neutropenia (5.2% *vs* 1.3%) while a lower frequency in the S95005 + bevacizumab group was reported for palmar-plantar syndrome (none *vs* 11.8%) and diarrhoea (1.3% *vs* 6.6%).

EAEs leading to IMP withdrawal were reported with a similar frequency in the two groups: 42.9% in the S95005 + bevacizumab group *vs* 42.1%. Of those EAEs, the most frequent was malignant neoplasm progression: 13.0% *vs* 17.1% Other EAEs leading to IMP withdrawal occurred in a single patient in the two groups, except palmar-plantar syndrome (none in the S95005 + bevacizumab group *vs* 3 patients, including 2 severe, in the capecitabine + bevacizumab group), neutropenia (2 patients *vs* none, not severe), acute kidney injury (2 *vs* 1 patient, all severe), asthenia (none *vs* 2 patients, not severe) and intestinal obstruction (none vs 2 patients, all severe).
Each treatment-related EAE leading to IMP withdrawal occurred in a single patient, except neutropenia (2 patients *vs* none) and palmar-plantar syndrome (none *vs* 3 patients).

EAEs leading to dose delay (71.4% *vs* 44.7%) or dose reduction (19.5% *vs* 35.5%) were mainly:

- In the S95005 + bevacizumab group: neutropenia and neutrophil count decreased. Those two EAEs led to dose delay in 44.2% *vs* 2.6% in the capecitabine + bevacizumab group and 27.3% *vs* 2.6%, respectively, and led to dose reduction in 5.2% *vs* 1.3% and 5.2% *vs* none, respectively.
- In the capecitabine + bevacizumab group: palmar-plantar syndrome leading to dose delay in 18.4% of patients *vs* none in the S95005 + bevacizumab group and dose reduction in 21.1% *vs* none, respectively.

The frequency of ***serious EAEs*** was similar in the two groups: 66.2% *vs* 59.2%. The most frequent SEAEs were malignant neoplasm progression in both groups: 16.9% *vs* 21.1%. Other SEAEs reported in more than 2 patients were as follows:

- In the S95005 + bevacizumab group: neutropenia, anaemia, pneumonia (5.2% for each), intestinal obstruction, febrile neutropenia, peritonitis, pulmonary embolism, acute kidney injury, hypertension and dehydration (3.9% for each).
- In the capecitabine + bevacizumab group: diarrhoea (7.9%), dehydration (6.6%), deep vein thrombosis (5.3%), febrile neutropenia and pulmonary embolism (3.9% for both).

Treatment-related SEAEs reported in more than 2 patients were neutropenia (5.2% in the S95005 + bevacizumab group *vs* none in the capecitabine + bevacizumab group), febrile neutropenia (3.9% *vs* 1.3%), diarrhoea (2.6% *vs* 7.9%), dehydration (2.6% *vs* 3.9%), pulmonary embolism and deep vein thrombosis (none *vs* 3.9%, each).
During the study, death was reported for 132 patients, 66 in each group *i.e.* 85.7% in the S95005 + bevacizumab group and 86.8% in the capecitabine + bevacizumab group. Of those, 4 patients (5.2%) *vs* 9 patients (11.8%), respectively, died during the treatment period. The reason of death was mostly progressive disease (81.8% of all deaths) with the same frequency in each treatment group.
All patients who died during the treatment period experienced at least one fatal EAE, except 1 patient in the capecitabine + bevacizumab group who died from progressive disease without reporting an adverse event.

- **Blood laboratory tests**

For ***biochemistry parameters***, emergent severe abnormal values (Grade ≥ 3) were sparse in the two groups for each parameter, except for high GGT (10.8% in the S95005 + bevacizumab group *vs* 1.3% in the capecitabine + bevacizumab group).
For ***haematological parameters***, the most frequent emergent severe abnormal values were detected with a higher frequency in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group for low neutrophils (63.5% *vs* 9.5 %), low WBC (36.0% *vs* 9.2%) and low lymphocytes (22.2%, *vs* 10.7%). Regarding severe low neutrophils in the S95005 + bevacizumab group, the median number of days to recovery was 9.0 days.

- **Other safety evaluation**

At final analysis, updated results were similar to those at primary analysis.

CONCLUSION

In this non-comparative phase 2 study, 153 patients were included and randomised to evaluate S95005 + bevacizumab and capecitabine + bevacizumab in the first-line treatment of patients with previously untreated unresectable mCRC, and who were non eligible for intensive therapy.

As shown in the earlier primary PFS analysis, the median PFS was unchanged: 9.2 months in the S95005 + bevacizumab group and 7.8 months in the capecitabine + bevacizumab group. At the end of study, the data for OS were mature for final analysis. The median OS followed a trend consistent with PFS results: 22.3 months in the S95005 + bevacizumab group and 17.7 months in the capecitabine + bevacizumab group. The hazard ratio between the two treatment groups was 0.78, with 95%CI = [0.55, 1.10].

At final analysis, updated safety data were consistent with that previously reported at the primary analysis. The safety profile of S95005 in combination with bevacizumab was characterised by hematologic and gastrointestinal most frequent emergent adverse events (EAE). Treatment-related neutropenia were reported in 54.5% of patients in the S95005 + bevacizumab group and 5.3% in the capecitabine + bevacizumab group, mostly were severe (46.8% *vs* 2.6%, respectively). Febrile neutropenia was reported with similar frequency in both treatment groups and all these events resolved. In the capecitabine + bevacizumab group, the most frequent EAE was palmar-plantar syndrome reported in 52.6% of patients (3.9% in the S95005 + bevacizumab group), mostly treatment-related, as well as gastrointestinal adverse events. Overall, severe treatment-related EAEs were more frequently reported in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (77.9% *vs* 43.4%, respectively), mostly due to myelosuppressive events, as expected. EAEs leading to treatment withdrawal were reported with a similar frequency in the two treatment groups: 42.9% in the S95005 + bevacizumab group *vs* 42.1%.

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