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. The description of the study protocol given hereafter includes the modifications of the 4 substantial amendments to the protocol.		
Main coordinator [redacted] Belgium.		
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): Mayer RJ *et al*. RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14; 372(20) : 1909-19.		
Studied period (event driven trial): Initiation date: 29 April 2016 (date of first visit patient) Completion date: 15 January 2018 (cutoff date for the 100th progression-free survival event (progression of disease or death))	**Phase of development of the study:** 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) [The European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ)-C30 and QLQ-CR29]. **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 were 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 (PS; 0 *versus* 1 *versus* 2) and country.

Once 100 PFS events were reached, the main analysis was performed and is presented in the present clinical study report. The on-going patients had to continue the study without change until the end of the study.

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

Number of patients:
Planned: 150 patient in total (75 patients per group)
Included: 153 patients (77 patients in the S95005 + bevacizumab group and 76 patients in the capecitabine + bevacizumab group).
Number of primary events: 100 PFS events

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 KRAS and NRAS Exon 2: codon 12 and 13 determined), 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 (tablet) + bevacizumab (IV solution)
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 (tablet) + bevacizumab (IV solution)
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 but could not be lower.

Duration of treatment:

Screening period and inclusion: up to 28 days prior to inclusion visit/randomisation.
Treatment period: each patient had to receive at least 28 days of combination of S95005+ bevacizumab or at least 21 days 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. Patients were considered to be on treatment as long as either component of the combination regimen continued to be administered unless the investigator judged that it was in the interest of the patient to withdraw from the study and to be treated outside of this protocol with a combine modality.
Follow-up period: after the end of the treatment period until the end of the study (12 months after the follow-up start date of the last patient withdrawn), for patients who discontinued study treatment for reasons other than radiologic disease progression (*e.g.*, intolerable side effects), patients were followed for tumour response until radiologic disease progression or death, or initiation of new anticancer therapy (whichever occurred first); for patients who discontinued study treatment for progression disease, patients 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).

Secondary endpoints: ORR based on Investigator review of the images according to RECIST 1.1, DR, Disease DCR, OS, and QoL assessed by 2 QLQs [Core questionnaire (EORTC QLQ-C30) and CRC-specific module (QLQ-CR29)] every 12 weeks.

Of note: the tumor marker Carcinoembryonic Antigen was considered as an efficacy measurement according to the study protocol and is presented as such in the present study report.

Safety measurements:

The following safety and tolerability criteria were defined as secondary endpoints and were assessed by:

- Incidence of Adverse Events (AEs), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Events Requiring Immediate Notification (ERIN) not related to the research were reported during the 100 days after the last study drug intake and the serious AEs (SAEs) related to the research were reported without any time delay.
- Laboratory tests: haematology, blood biochemistry, coagulation, urinalysis.
- Physical examination and ECOG PS.
- Vital signs: blood pressure (BP), heart rate, body temperature, respiration rate, body weight.
- 12-leads ECG parameters.

Biomarkers measurements:

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

Statistical methods:

Analysis Set:

- **Randomised Set (RS):** all patients to whom a therapeutic unit was randomly assigned using the IWRS.
- **Full Analysis Set (FAS):** all randomised patients who have taken at least one dose of Investigational Medicinal Product (IMP).
- **Per Protocol Set (PPS**): all patients of the FAS without relevant deviation(s), which could affect the evaluation of the IMP effect on the primary efficacy endpoint.
- **Tumor Response (TR) Population**: all patients in the PPS with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment (with the same method of measurement as baseline). Patients who had a cancer-related death prior to their first tumor evaluation were also considered evaluable with Progressive Disease (PD) as best overall response.
- **Safety Set (SS):** all patients who received at least one dose of IMP.
- **Quality of Life Set (QLS)**: patients should have completed at least two third of the questions of the baseline QLQ-C30 questionnaire, and at least two third of the questions of a QLQ-C30 questionnaire during the study period. Conditions were the same for the QLQ-CR29 questionnaires.
- **Archived tumor biopsies Full Analysis Set (TUMFAS**): all patients from the FAS population with an analyzable value based on archived tumor biopsy.
- **Archived tumor biopsies Tumor Response Set (TUMTR**): all patients from the FAS population with an analyzable value based on an archived tumor biopsy.
- **Serum Full Analysis Set (SERFAS):** all patients from the FAS population with an analyzable value at baseline based on serum sample.

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 *versus* 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 survival probabilities at 6, 12, 18, and 24 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.

Of note, for all other criteria (study outcome, secondary efficacy endpoints, safety), a data selection algorithm based on the date of 20 January 2018 was used in order to define which data should be retained.

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 tumor response (TR) population.

DCR and ORR based on 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.

Biomarkers: analyses of markers by ImmunoHistoChemistry [IHC: Thymidine Phosphorylase (TP), thymidine kinase (TK) and thymidylate synthase (TS) according to PFS and response (DCR/ORR) were performed. For microsatellites, analyses according to response could not be performed due to less than 10 MSI-H (high microsatellite instability) patients. Contingency tables were provided in each arm comparing the mutation status obtained in central laboratory with blood Polymerase Chain Reaction (PCR) to the mutation status obtained locally with a tumor biopsy.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Table 1 – Disposition of patient and analysis sets

Status		S95005 + bevacizumab (N = 77)	Capecitabine + bevacizumab (N = 76)	All (N = 153)
Included*	**n**	**77**	**76**	**153**
Withdrawn due to	**n (%)**	**56 (72.7)**	**59 (77.6)**	**115 (75.2)**
progressive disease	n (%)	29 (37.7)	38 (50.0)	67 (43.8)
adverse event	n (%)	17 (22.1)	14 (18.4)	31 (20.3)
non-medical reason	n (%)	8 (10.4)	2 (2.6)	10 (6.5)
physician decision	n (%)	2 (2.6)	5 (6.6)	7 (4.6)

** one patient was randomised but not included and did not receive any study drug; % Expressed as percentage of the patients from the Included Set by group*

Analysis sets		S95005 + bevacizumab (N = 77)	Capecitabine + bevacizumab (N = 77)	All (N = 154)
Randomised Set (RS)	**n**	**77**	**77**	**154**
Full Analysis Set (FAS)	**n**	**77**	**76**	**153**
Quality of Life Set 29 (QLS29)	n (%)	60 (77.9)	57 (75.0)	117 (76.5)
Quality of Life Set 30 (QLS30)	n (%)	62 (80.5)	59 (77.6)	121 (79.1)
Archived Tumour biopsy FAS (TUMFAS)	n (%)	48 (62.3)	45 (59.2)	93 (60.8)
Serum FAS (SERFAS)	n (%)	73 (94.8)	69 (90.8)	142 (92.8)
Per Protocol Set (PPS)	n (%)	76 (98.7)	76 (100)	152 (99.3)
Tumor Response Set (TR)	n (%)*	74 (97.4)	73 (96.1)	147 (96.1)
Archived Tumour biopsy TR Set (TUMTR)	n (%)*	46 (60.5)	43 (56.6)	89 (58.6)
Safety Set	**n**	**77**	**76**	**153**

*% % of the FAS; * % of the PPS*

SUMMARY – CONCLUSIONS (Cont'd)

BASELINE CHARACTERISTICS (Cont'd)

Demographic and other baseline characteristics were globally in line with inclusion criteria defined in the study protocol. In the RS, the median age was 75.0 years. Patients > 75 years were more frequent than patients ≤ 65 and]65;75] years in the capecitabine + bevacizumab group (50.7% *versus* 23.4% and 26.0%, respectively), while the age class distribution was well balanced in the S95005 + bevacizumab group (≤ 65 years: 27.3%,]65;75]: 36.4% and > 75: 36.4%). Overall, 57.1% of patients were male and 96.7% of patients were white. The proportion of male was lower in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (52.0% *versus* 62.3%). The treatment groups were well balanced with respect to BRAF, NRAS and KRAS status.

At baseline, all patients were diagnosed with metastases of colorectal cancer, confirmed with histology or cytology, and all patients had at least one measurable metastatic lesion. The primary tumour site was more frequently the right colon in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (39.0% *versus* 24.7%). At the time of inclusion, the mean duration from CRC diagnosis was longer in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 1.5 ± 2.8 *versus* 1.2 ± 1.6 year. Of note, for 15 patients (9 patients in the S95005 + bevacizumab group and 6 in the capecitabine + bevacizumab group), mCRC duration was > 6 months and these patients were considered to have a protocol deviation at inclusion. At study entry, less than half of the patients (22.7%) were in relapse of mCRC. Overall, 114 patients (74.0%) received at least one previous therapy for mCRC, mostly surgery in 111 patients (72.1%); there was no relevant difference between the two groups, except that drug treatments (all adjuvant and/or neo-adjuvant) were more frequently received in patients from the S95005 + bevacizumab group than in those from the capecitabine + bevacizumab group (32.5% *versus* 22.1%).

Regarding vital signs (ECOG PS, weight, BSA, supine blood pressure and heart rate), no relevant between-group differences was detected at baseline. Most of patients had an ECOG PS rated 0 or 1 (0: 34.6%, 1: 49.7%, 2: 15.7%).

EXTENT OF EXPOSURE

In the SS, due to the length difference of the cycles between the two arms, the mean number of cycles was lower in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 7.8 ± 4.2 *versus* 9.4 ± 6.0 cycles, and the maximum number of cycles reached was also lower (18 and 25 cycles, respectively). The mean treatment duration was higher in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 34.9 ± 20.0 weeks *versus* 29.2 ± 19.2 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% *versus* 73.7%. The number of cycles delayed by patient was higher in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (median: 3.0 *versus* 1.0). On the other hand, the percentage of patients who had at least one cycle with dose reduced was lower in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: 40.3% *versus* 48.7%.

The relative dose intensity (RDI) of IMP was lower in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (80.7 ± 15.7% *versus* 85.3 ± 15.9%, respectively). With regard to the RDI of bevacizumab, it was also lower in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (83.3 ± 13.1% *versus* 95.5 ± 11.7%, respectively). More than half of the patients had an RDI of IMP above 80%, with a lower frequency reported in the S95005 + bevacizumab group in comparison with the capecitabine + bevacizumab group: 55.8% *versus* 64.5%, respectively.

EFFICACY RESULTS

- **Primary efficacy endpoint**

The primary analysis of the primary endpoint (PFS) was performed at the cutoff date, which took into account the 100th PFS event. In the FAS, the median PFS in the S95005 + bevacizumab group was 9.2 months and 7.8 months in the capecitabine + bevacizumab group. When comparing the two PFS, the HR was 0.71, 95%CI = [0.48, 1.06], 80%CI = [0.55, 0.92]. A trend to a better PFS was observed in the S95005 + bevacizumab group in comparison with the capecitabine + bevacizumab group.

The probability of PFS was greater at each time-point evaluated (2, 4, 6, 12 months) in the S95005 + bevacizumab group in comparison with the capecitabine + bevacizumab group, and was 0.37 vs 0.28 at 1 year. The results in the PPS were similar to those in the FAS. Regarding PFSs1 (PFS taking in account further new anti-cancer therapy as an event of progressive disease) and PFSs2 (PFS taking in account clinical progression) both showed median values and HRs comparable to those of PFS.

An exploratory subgroup analysis based on stratification factors and predefined subgroups showed a longer PFS in the S95005 + bevacizumab group compared to the capecitabine + bevacizumab group for most of the subgroups. A trend to more pronounced treatment effect was found in the following subgroups: RAS mutant, female, absence of surgical resection and location of primary disease on the left colon.

- **Secondary efficacy endpoints**

  - ***Overall response rate, disease control rate***

In the FAS, the ORR was 33.8% in the S95005 + bevacizumab group and 30.3% in the capecitabine + bevacizumab group. DCR was 85.7% and 77.6%, respectively. The frequency of patients having confirmed partial response was 33.8% in the S95005 + bevacizumab group and 30.3% in the capecitabine + bevacizumab group, for stable disease (SD): 52.0% and 47.4%, respectively, and for PD: 5.2% and 15.8%, respectively. Similar results were observed in the TR population.

  - ***Duration of response***

In the TR, the median DR was 7.9 months in the S95005 + bevacizumab group and 9.9 months in the capecitabine + bevacizumab group. The comparison of the two groups led to a HR = 1.16, 95%CI = [0.49, 2.74], and 80% CI = [0.66, 2.03].

  - ***Overall survival***

In the FAS, at the cutoff date, overall survival data were not mature but followed a trend consistent with the PFS. In the S95005 + bevacizumab group, the OS was 18.0 months and 16.2 months in the capecitabine + bevacizumab group. The comparison of the two groups led to an HR of 0.56, 95%CI = [0.32, 0.98], 80%CI = [0.39, 0.80]. The Kaplan Meier curves showed that the survival probability was higher in the S95005 + bevacizumab compared to the capecitabine + bevacizumab group, and at 1-year post baseline, the survival probability was 0.77 in the S95005 + bevacizumab group and 0.67 in the capecitabine + bevacizumab group.

  - ***Carcinoembryonic Antigen (CEA)***

Emergent abnormal CEA values on treatment were observed with a similar frequency in both treatment groups (7.8% in the S95005 + bevacizumab group *versus* 8.1% in the capecitabine + bevacizumab group). CEA values which were abnormal at baseline normalised on treatment in 12.5% of patients in the S95005 + bevacizumab group and 6.5% of patients in the capecitabine + bevacizumab group.

- **Quality of life**

QLQ-C30 questionnaire showed no clinically relevant difference (minimally important difference of ± 10 points) on treatment in mean change of score from baseline for the global health status, functioning scales, and for most of the symptom scales, except for nausea/vomiting and diarrhoea (worsening in the S95005 + bevacizumab group and stable in the capecitabine + bevacizumab group for both symptoms), fatigue (stable in the S95005 + bevacizumab group and worsening in the capecitabine + bevacizumab group), loss appetite (worsening in the two groups) and insomnia (improvement in the two groups).

QLQ-CR29 questionnaire showed no clinically relevant difference on treatment in mean change of score from baseline for most of items except for the following: hair loss, trouble with taste (worsening for both symptoms in the S95005 + bevacizumab group while stable for hair loss and improvement for trouble with taste in the capecitabine + bevacizumab group), sore skin, dry mouth (stable in the S95005 + bevacizumab group and worsening in the capecitabine + bevacizumab group for both symptoms) and anxiety (stable in the S95005 + bevacizumab group and improvement in the capecitabine + bevacizumab group).

EFFICACY RESULTS (Cont'd)

- **Protein biomarkers by IHC (TP, TS, TK)**

There was a stronger difference in terms of PFS in favor of S95005 + bevacizumab group over capecitabine + bevacizumab group in TUMFAS (median = 9.9 months *versus* 6.0 months, HR = 0.43, 95%CI = [0.26, 0.72], 80%CI = [0.31, 0.61]) than in FAS, consequently the TUMFAS might not be a representative subset of the FAS. The biomarker results presented hereafter should be then interpreted with caution.

In TUMFAS, for TP marker, an effect on PFS was observed in favor of S95005 + bevacizumab over capecitabine + bevacizumab whichever the biomarker group (bmk+/bmk-), regardless of the cutoff considered (from 5% to 35%). Additionnally, even though there was always an effect in favor of S95005 + bevacizumab over capecitabine + bevacizumab, this trend was stronger in S95005 + bevacizumab over capecitabine + bevacizumab within bmk- patients, whichever the cutoff considered. Analysis of the interaction of biomarker class at cutoff 5% (bmk+/bmk-) and treatment was statistically significant (p value = 0.034). Hence, patients belonging to bmk- class had a better PFS in S95005 + bevacizumab over capecitabine + bevacizumab group.

For TS marker, a comparable effect on PFS in favor of S95005 + bevacizumab was observed whatever the biomarkers occupancy class. For TK1 marker, an effect on PFS in favor of S95005 + bevacizumab was observed in patients of the bmk+ group, regardless of the cutoff. This difference was only due to a lower PFS for patients with bmk+ in the capecitabine + bevacizumab group.

SAFETY RESULTS

- **Emergent adverse events**

The main results of AEs in the Safety Set based on the date of 20 January 2018 are summarised in Table 2.

Table 2: Overall summary for adverse events based on the date of 20 January 2018 in the Safety Set (N = 153)

		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* EAE	n (%)	68 (88.3)	53 (69.7)
Treatment-related	n (%)	60 (77.9)	33 (43.4)
Serious AE (including death)	n (%)	42 (54.5)	45 (59.2)
Serious EAE (including death)	n (%)	42 (54.5)	44 (57.9)
Treatment-related	n (%)	25 (32.5)	17 (22.4)
EAE leading to treatment withdrawal	n (%)	31 (40.3)	28 (36.8)
Severe* EAE	n (%)	21 (27.3)	20 (26.3)
Serious EAE	n (%)	19 (24.7)	17 (22.4)
Treatment-related EAE	n (%)	14 (18.2)	11 (14.5)
Treatment-related serious EAE	n (%)	9 (11.7)	4 (5.3)
Treatment-related severe* EAE	n (%)	9 (11.7)	7 (9.2)
Patients who died during the study	n (%)	22 (28.6)	33 (43.4)
During treatment period	n (%)	4 (5.2)	9 (11.8)
During the follow-up period	n (%)	18 (23.4)	24 (31.6)

**CTCAE grade 3 or 4*

Overall, most of the patients reported at least one EAE. In the S95005 + bevacizumab group, the most affected SOCs were Gastrointestinal disorders and Blood and lymphatic system disorders, both with a higher frequency than in capecitabine + bevacizumab group (81.8% *versus* 67.1% and 72.7% *versus* 19.7%, respectively). Among the other SOCs, the frequency of EAEs was comparable between the two groups, except for the following (with a difference between the groups > 10%): Skin and subcutaneous tissue disorders with a lower frequency in the S95005 + bevacizumab group *versus* capecitabine + bevacizumab group (27.3% *versus* 61.8%), and the following SOCs reported with a higher frequency in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: Infections and infestations (50.6% *versus* 38.2%), Investigations (54.5% *versus* 36.8%), and Metabolism and nutrition disorders (50.6% *versus* 31.6%).

SAFETY RESULTS (Cont'd)

The ***most commonly reported EAEs*** (≥ 20% of patients) in the S95005 + bevacizumab group were neutropenia (53.2% *versus* 6.6% in the capecitabine + bevacizumab group), diarrhoea (53.2% *versus* 43.4%), nausea (46.8% *versus* 18.4%), decreased appetite (37.7% *versus* 19.7%), fatigue (36.4% *versus* 30.3%), anemia (31.2% *versus* 6.6%), vomiting (28.6% *versus* 11.8%), neutrophil count decreased (23.4% *versus* 11.8%), malignant neoplasm progression (22.1% *versus* 25.0%), and alopecia (22.1% *versus* none). These EAEs more frequently affected patients in the S95005 + bevacizumab group, except for malignant neoplasm progression. In the capecitabine + bevacizumab group, the most frequent EAE was palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome), reported in 52.6% of patients *versus* 3.9% in the S95005 + bevacizumab group, and the other most frequent EAEs were diarrhoea, fatigue, malignant neoplasm progression (see above), asthenia (18.2% in the S95005 + bevacizumab group *versus* 22.4% in the capecitabine + bevacizumab group), and stomatitis (16.9% *versus* 21.1%, respectively).

Patients affected by at least one ***severe EAE*** (Grade ≥ 3) were more frequent in the S95005 + bevacizumab group in comparison with the capecitabine + bevacizumab (88.3% *versus* 69.7%). In the S95005 + bevacizumab group, the most frequent (> 10%) severe EAEs were reported with higher frequency in the S95005 + bevacizumab group in comparison with the capecitabine + bevacizumab group, except for malignant neoplasm progression. They were neutropenia (46.8% *versus* 5.3%), anaemia (10.4% *versus* none), neutrophil count decreased (18.2% *versus* 1.3%), white blood cell (WBC) count decreased (10.4% *versus* 2.6%), malignant neoplasm progression (13.0% *versus* 21.1%) and hypertension (13.0% *versus* 5.3%).
In the S95005 + bevacizumab group, neutropenia was either Grade 3 (22.1%) or Grade 4 (24.7%) and neutrophil count decreased was Grade 3 (14.3%) or Grade 4 (3.9%). Febrile neutropenia was reported in 4 patients (5.2%); these EAEs were all severe (Grade 3, 2 patients and Grade 4, 2 patients) and all recovered.
In the capecitabine + bevacizumab group, the most frequent severe EAEs were malignant neoplasm progression (21.1% with 3.9% Grade 3, 1.3% Grade 4 and 15.8% fatal) and palmar-plantar syndrome (11.8% all Grade 3). Three patients experienced febrile neutropenia (Grade 3 in 2 patients and Grade 4 in 1 patient) and all the concerned patients recovered.

Most of the patients had at least one ***treatment-related EAE*** (to IMP and/or bevacizumab) in the two groups, with a higher frequency reported in the S95005 + bevacizumab than in the capecitabine + bevacizumab: 97.4% *versus* 89.5%. In the S95005 + bevacizumab group, the most frequently (> 20%) treatment-related EAEs were the following with a higher frequency reported in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group: neutropenia (53.2% *versus* 3.9%), anaemia (22.1% *versus* 5.3%), neutrophil count decreased (22.1% *versus* 2.6%), diarrhoea (40.3% *versus* 35.5%), nausea (40.3% *versus* 14.5%), vomiting (22.1% *versus* 9.2%), fatigue (31.2% *versus* 26.3%) and decreased appetite (29.9% *versus* 17.1%). In the capecitabine + bevacizumab group, the most frequently reported treatment-related EAE was palmar-plantar syndrome with a lower frequency in the S95005 + bevacizumab group (3.9% *versus* 51.3% in the capecitabine + bevacizumab group). The other most frequent treatment-related EAEs in the capecitabine + bevacizumab group were stomatitis (16.9% in the S95005 + bevacizumab group *versus* 21.1% in the capecitabine + bevacizumab group), diarrhoea and fatigue (see above). Among the ten most frequently treatment-related EAEs in the S95005+ bevacizumab group, the majority were of Grade 1 or Grade 2 (as worst grade), except neutropenia (6.5% Grade 2, 22.1% Grade 3, 24.7% Grade 4) and neutrophil count decreased (5.2% Grade 2, 13% Grade 3, 3.9% Grade 4). Among the ten most treatment-related EAEs in the capecitabine + bevacizumab group, the majority were rated Grade 1 or Grade 2.
Overall, severe treatment-related EAEs were reported with a higher frequency in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group (77.9% *versus* 43.4%). Such higher frequency was observed for neutropenia (46.8% *versus* 2.6%, respectively), neutrophil count decreased (16.9% *versus* 1.3%), WBC count decreased (10.4% *versus* 1.3%), hypertension (6.5% *versus* 3.9%), anaemia (6.5% *versus* none) and febrile neutropenia (5.2% *versus* 1.3%). The frequency of severe treatment-related was lower in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group for palmar-plantar syndrome (none *versus* 11.8%) and diarrhoea (1.3% *versus* 6.6%).

SAFETY RESULTS (Cont'd)

EAEs leading to IMP withdrawal were reported with a similar frequency in the two treatment groups: in the S95005 + bevacizumab group *versus* 36.8% in the capecitabine + bevacizumab group. The most frequent EAEs leading to IMP withdrawal were malignant neoplasm progression in the two groups: 13.0% in the S95005 + bevacizumab group *versus* 15.8% in the capecitabine + bevacizumab group. Other EAEs leading to IMP withdrawal were sparsely distributed in the two groups with a single patient for each EAE, except diarrhoea, and acute kidney injury (2 patients each) in the S95005 + bevacizumab group, and palmar-plantar syndrome (3 patients) and asthenia (2 patients) in the capecitabine + bevacizumab group. Severe EAEs leading to IMP withdrawal (27.3% *versus* 26.3%) occurred in a single patient, except for malignant neoplasm progression (6 patients, 7.8%, *versus* 9 patients, 11.8%, respectively), acute kidney injury (2 patients, 2.6% *versus* 1 patient, 1.3%) and palmar-plantar syndrome (none *versus* 2 patients, 2.6%). All treatment-related EAEs leading to IMP withdrawal occurred in a single patient except palmar-plantar syndrome (3 patients, 3.9%, in the capecitabine + bevacizumab group including 2 patients, 2.6%, with severe palmar-plantar syndrome) and diarrhoea (2 patients, 2.6%, in the S95005 + bevacizumab group). Treatment-related EAEs leading to IMP withdrawal were severe in 11.7% *versus* 9.2% of the patients.

EAE leading to ***dose delay*** (52 patients, 67.5% in the S95005 + bevacizumab group and 31 patients, 40.8% in the capecitabine + bevacizumab group), to ***dose reduction*** (15 patients, 19.5% and 24 patients, 31.6%, respectively), or to ***dose delay and dose reduction*** (17 patients, 22.1% and 7 patients, 9.2%, respectively) were mainly:

- In the S95005 + bevacizumab group, neutropenia and neutrophil count decreased: 44.2% and 23.4% of patients, respectively (*versus* none in the capecitabine + bevacizumab group) with these EAEs leading to dose delay, 5.2% for each (*versus* 1.3% and none, respectively, in the capecitabine + bevacizumab group) leading to dose reduction, and 15.6% and 6.5%, respectively, (*versus* none in the capecitabine + bevacizumab group) leading to dose delay and dose reduction,
- In the capecitabine + bevacizumab group, palmar-plantar syndrome: 18.4% of patients (*versus* none in the S95005 + bevacizumab group) with this EAE leading to dose delay, 21.1% (*versus* none) leading to dose reduction, and 6.6% (*versus* none) leading to dose delay and dose reduction.

The frequency of ***serious EAEs*** (including death as preferred term) was similar in the two groups (54.5% in the S95005 + bevacizumab group *versus* 57.9% in the capecitabine + bevacizumab group). The most frequent SEAEs were malignant neoplasm progression in both groups: 10.4% *versus* 21.1%. SEAEs reported in more than 2 patients were as follows:

- In the S95005 + bevacizumab group, neutropenia (4 patients, 5.2%), febrile neutropenia, anaemia, pneumonia, pulmonary embolism, hypertension, and dehydration (3 patients, 3.9% each).
- In the capecitabine + bevacizumab group, diarrhoea and dehydration (5 patients, 6.6% each), deep vein thrombosis (4 patients, 5.3%), febrile neutropenia and pulmonary embolism (3 patients, 3.9% each).

Treatment-related (to IMP and/or bevacizumab) SEAEs in more than 2 patients were febrile neutropenia (3.9% *versus* 1.3%), neutropenia (5.2% *versus* none), diarrhoea (2.6% *versus* 6.6%) dehydration (2.6% *versus* 3.9%), and pulmonary embolism (none *versus* 3.9%).

Based on the date of 20 January 2018, deaths had been reported for 55 patients (36.0%): 22 patients (28.6%) in the S95005 + bevacizumab group and 33 patients (43.4%) in the capecitabine + bevacizumab group, of which 4 patients, 5.2%, and 9 patients, 11.8%, died during the treatment period. The most frequently reported reason of death was progressive disease in 39 patients: 72.7% of deaths in the S95005 + bevacizumab group *versus* 69.7% of deaths in the capecitabine + bevacizumab group. Among the patients who died during the treatment period, all experienced at least one fatal EAE (4 patients, 5.2% in the S95005 + bevacizumab group *versus* 8 patients, 10.5% in the capecitabine + bevacizumab group), except 1 who died from progressive disease without reporting EAE.

Blood laboratory evaluation

For the **biochemistry parameters**, emergent severe abnormal values (Grade ≥ 3) were sparse in the two groups and for each parameter, except for high GGT (8.1% in S95005 + bevacizumab group *versus* 2.7% in capecitabine + bevacizumab group), low phosphate (8.2% *versus* 2.7%), high magnesium (6.8%*versus* 3.4%), low sodium (5.3% in both groups) and high glucose (1.4%, *versus* 6.9%).

For the **hematological parameters,** 62.2% of patients experienced emergent Grade ≥ 3 low neutrophils values in the S95005 + bevacizumab group and 32.0% experienced low WBC on treatment, while Grade ≥ 3 values were observed for each of these two parameters in 9.5% in the capecitabine + bevacizumab group. Low lymphocytes (19.2% *versus* 8.0%), low platelets (4.0% *versus* 1.3%) and low hemoglobin (12.0% *versus* none) were also more frequent in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group. Regarding patients who experienced emergent severe low neutrophils in the S95005 + bevacizumab group, the median number of days to recovery (*i.e.* Grade < 2 or ≤ baseline grade) was 8.5 days.

Other safety evaluation

There was no relevant difference between the two groups in mean changes for weight, blood pressure and heart rate. A higher median decrease in systolic blood pressure was observed in the S95005 + bevacizumab group compared to the capecitabine + bevacizumab group (-17.0 mmHg *versus* -10.5 mmHg).

The majority of the patients in both treatment groups had their baseline ECOG PS maintained during the study (55.8% in the S95005 + bevacizumab group *versus* 52.6% in the capecitabine + bevacizumab group). A worsening of ECOG PS on treatment by at least one grade from baseline was reported with similar frequency in the two treatment groups (37.7% *versus* 38.2%, respectively). Emergent ECOG PS value equal to 3 on treatment occurred in 1.3% in the S95005 + bevacizumab group *versus* 8.1% in the capecitabine + bevacizumab group. The median time to ECOG PS worsening* was 10.9 and 11.1 months, respectively *(* from ECOG PS = 0-1 at baseline to ≥ 2 post-baseline, or from ECOG PS = 2 at baseline to ≥ 3 post-baseline).*

CONCLUSION

This study was an open-label, two-arm, randomised, non-comparative phase 2 study evaluating 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.

The primary efficacy analysis was performed at the cutoff date based on the occurrence of 100 Progression Free Survival (PFS) events among the 153 treated patients. The PFS in the S95005 + bevacizumab group was 9.2 months and 7.8 months in the capecitabine + bevacizumab group. When comparing the two groups, the hazard ratio (HR) was 0.71, 95% CI = [0.48, 1.06]. Therefore, a trend to a better PFS was observed in the S95005 + bevacizumab group compared to the capecitabine + bevacizumab group, as well as a similar trend for disease control rate. At the cutoff date, overall survival data were not mature but were consistent with PFS. The median overall survival was 18.0 months and 16.2 months, respectively. The comparison of the two groups led to a HR = 0.56, 95%CI = [0.32, 0.98].

The safety profile of S95005 in combination with bevacizumab was in line with the one known either as monotherapy or as combination with bevacizumab, characterised by hematologic, gastrointestinal, and fatigue, as main adverse events. In the S95005 + bevacizumab group, 53.2% of patients experienced neutropenia related to treatment, mostly of Grade 3 or 4 (3.9% in the capecitabine + bevacizumab group). Febrile neutropenia was reported with similar frequency in both treatment groups and all of these events resolved. In the capecitabine + bevacizumab group, the most frequent emergent adverse event was palmar-plantar erythrodysaesthesia syndrome reported in 52.6% of patients (3.9% in the S95005 + bevacizumab group), mostly treatment-related, and gastrointestinal events. Overall, severe treatment-related EAEs were more frequently reported in the S95005 + bevacizumab group than in the capecitabine + bevacizumab group, mostly due to myelosuppressive events, expected. The majority of the patients had their ECOG PS maintained throughout the study, and global scores on quality of life questionnaires did not show relevant change over time.

These data warranted to be confirmed through a comparative phase 3 study.

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