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ORIGINAL ARTICLE

Maintenance with 5-FU/LV-aflibercept after induction with FOLFIRI-aflibercept versus FOLFIRI-aflibercept until progression as second-line treatment in older adults with metastatic colorectal cancer: the AFEMA phase II randomized trial

P. García-Alfonso[1†*], E. Elez[2], J. Soto-Alsar[1], D. Páez[3], A. Fernández-Montes[4], B. Graña[5], A. Salud[6], A. Yubero[7], M. A. Gómez-España[8], I. Macías[9], G. Quintero[10], C. López-López[11], T. Fernández-Rodríguez[12], C. Grávalos[13], E. González-Flores[14], M. Guix[15], B. García Paredes[16], J. J. Reina[17], J. R. Rodríguez Mowbray[18], J. Sastre[16†] & E. Aranda[8], on behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

[1]Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Universidad Complutense, Madrid, Spain; [2]Medical Oncology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, CIBERONC, Barcelona, Spain; [3]Department of Medical Oncology, Hospital Santa Creu i Sant Pau, U705 CIBERER, Barcelona, Spain; [4]Department of Medical Oncology, Complexo Hospitalario Universitario de Ourense, Ourense, Spain; [5]Department of Medical Oncology, Complexo Hospitalario Universitario A Coruña, Instituto Investigación Biomédica INIBIC, A Coruña, Spain; [6]Department of Medical Oncology, Hospital Universitario Arnau de Vilanova de Lleida, Lleida, Spain; [7]Department of Medical Oncology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; [8]Department of Medical Oncology IMIBIC, Universidad de Córdoba, CIBERONC, Instituto de Salud Carlos III, Hospital Universitario Reina Sofía, Córdoba, Spain; [9]Department of Medical Oncology, Hospital Parc Taulí de Sabadell, Barcelona, Spain; [10]Department of Medical Oncology, Hospital Lucus Augusti, Lugo, Spain; [11]Department of Medical Oncology, Hospital Universitario Marqués de Valdecilla, IDIVAL, UNICAN, Santander, Spain; [12]Department of Medical Oncology, Hospital Son Llatzer, Palma de Mallorca, Spain; [13]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [14]Department of Medical Oncology, Hospital Virgen de las Nieves, Granada, Spain; [15]Department of Medical Oncology, Hospital del Mar, Barcelona, Spain; [16]Department of Medical Oncology, Hospital Clínico San Carlos, Instituto de Investigación Hospital Clínico San Carlos (IdISSC), Universidad Complutense, Madrid, Spain; [17]Department of Medical Oncology, Complejo Hospitalario Virgen de la Macarena, Sevilla, Spain; [18]Department of Medical Oncology, Hospital Virgen del Rocío, Sevilla, Spain

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Background: The combination chemotherapy i.v. 5-fluorouracil (5-FU), irinotecan, and aflibercept (FOLFIRI-A) is a standard second-line treatment of metastatic colorectal cancer (mCRC). The aim was to assess maintenance treatment in second-line setting in older patients (aged $\geq$70 years) with mCRC.

Patients and methods: We evaluated FOLFIRI-A given for six cycles followed by maintenance with 5-FU/leucovorin (LV)-A (arm A) or FOLFIRI-A (arm B) until progression in older adults with mCRC in the AFEMA randomized, open-label, non-inferiority phase II trial (EudraCT2016-004076-21/NCT03279289). Patients aged $\geq$70 years who previously failed oxaliplatin-fluoropyrimidine were randomly allocated (1 : 1) to either arm A (experimental) or arm B (control). After enrolling 35 patients, the FOLFIRI dose was reduced to level 1 in both arms due to toxicity. The primary endpoint was median progression-free survival (PFS); and secondary endpoints were median overall survival, objective response rate, and safety. Non-inferiority required the upper confidence interval (CI) limit to not exceed a hazard ratio (HR) of 1.5 (one-sided $\alpha = 0.075$, 80% power).

Results: A total of 170 patients were randomly allocated to arm A or arm B ($n = 85$ each). The median follow-up was 12.2 versus 10.9 months in arm A versus arm B. Most patients died (83.5% versus 88.2% in arm A versus arm B), mainly from disease progression. PFS non-inferiority was met (HR = 0.78, 95% CI 0.566-1.076, $P = 0.131$) with a median PFS of 6.1 versus 5.5 months in arm A versus arm B. Median overall survival was similar in arms A and B (12.2 and 11.5 months, respectively) (HR = 0.89, 95% CI 0.640-1.227, $P = 0.467$). During the maintenance phase, severe asthenia (4.5% versus 21.6%, $P = 0.038$), serious adverse events (SAEs) (17.8% versus 37.8%, $P = 0.049$), and treatment-related SAEs (6.7% versus 10.8%, $P = 0.695$) were reduced in arm A versus arm B.

Conclusion: In older adults, induction with six cycles of FOLFIRI-A plus maintenance with 5-FU/LV-A was non-inferior to FOLFIRI-A until progression. Severe asthenia, SAEs, and treatment-related SAEs were reduced with 5-FU/LV-A maintenance.

Key words: metastatic colorectal cancer, aflibercept, FOLFIRI, 5-FU, maintenance treatment

*Correspondence to: Prof. Pilar García-Alfonso, Servicio de Oncología Médica, Hospital Universitario Gregorio Marañón, C/Dr. Esquerdo, 46. 28007 Madrid, Spain. Tel: +34 676 01 55 01

E-mail: pgarcaalfonso@gmail.com (P. García-Alfonso).

†These authors contributed equally to this work.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of death among cancer patients.[1,2] Its incidence increases with age, affecting 16% of patients between the ages of 70 and 85 years in Europe in 2022.[3] One out of five patients with CRC have metastatic CRC (mCRC) at the time of diagnosis, and one out of two patients with localized CRC will develop mCRC.[4]

At the time of diagnosis, most patients receive a fluoropyrimidine as first-line therapy [e.g. i.v. 5-fluorouracil (5-FU) or oral capecitabine] combined with either oxaliplatin (FOLFOX or CAPOX) or irinotecan (FOLFIRI) and an antiangiogenic or anti-epidermal growth factor receptor (EGFR) therapy.[5] Additionally, induction chemotherapy followed by maintenance strategies has been shown to lower toxicity rates while maintaining efficacy in first-line advanced CRC treatment.[6-12] In a second-line setting, FOLFIRI combined with aflibercept (FOLFIRI-A) is a standard treatment of patients who did not respond to prior oxaliplatin treatment.[13] Although this treatment strategy has been shown to be as effective in patients aged ≥65 years as in younger patients, it has exhibited an increased toxicity.[14]

Older adults are historically underrepresented in most clinical trials.[15,16] Consequently, data from these trials may not accurately reflect this patient population in clinical practice, which tends to be older with more comorbidities, greater vulnerability, and a higher incidence of adverse events (AEs). As such, prospective clinical trials focusing on an older population are needed.

The AFEMA study aimed to determine whether induction with six cycles of FOLFIRI-A followed by maintenance with 5-FU/leucovorin (LV) plus aflibercept (5-FU/LV-A) was non-inferior to FOLFIRI-A given until progression in older adults with mCRC who have failed a prior oxaliplatin-fluoropyrimidine-based regimen.

MATERIAL AND METHODS

Detailed methods are provided in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103986.

Study design and patient eligibility

The AFEMA study was a phase II randomized, open-label, multicenter and non-inferiority trial (EudraCT2016-004076-21/NCT03279289). Patients aged ≥70 years with adenocarcinoma of the colon and/or rectum and mCRC that had progressed after a first-line oxaliplatin-fluoropyrimidine regimen were included (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103986). The study was conducted in 20 hospitals across Spain following the Declaration of Helsinki principles and was reviewed by the independent ethics committee. All patients gave their written informed consent before enrollment.

Treatment

Patients were randomly allocated (1 : 1) to receive six cycles of FOLFIRI-A (induction phase) followed by 5-FU/LV-A (maintenance phase) (arm A, experimental) or six cycles of FOLFIRI-A (induction phase) followed by the same schedule (maintenance phase) (arm B, control), both until disease progression (Figure 1). The standard dose of FOLFIRI was a 180 mg/m^2 i.v. infusion of irinotecan, 400 mg/m^2 i.v. infusion of LV, and a 5-FU 400 mg/m^2 i.v. bolus followed by a 2400 mg/m^2/46 h i.v. infusion of 5-FU. This full dose was poorly tolerated, however, and the protocol was amended (after including 35 patients) to initiate FOLFIRI at level 1 (modifications: irinotecan 150 mg/m^2, 5-FU 300 mg/m^2, and 5-FU 2000 mg/m^2/46 h). The standard dose level (if well tolerated) was subsequently increased according to the investigator's judgement. The initial dose of aflibercept was 4 mg/kg. Dose reductions, modifications, and/or delays are described in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103986. Patients were followed up after the end of their participation, at least once every 3 months until 12 months after inclusion of the last patient (according to the study protocol).

Outcomes and statistical analysis

The statistical design was based on a non-inferiority hypothesis with a similar median progression-free survival (mPFS) estimated at 6.6 months and a non-inferiority limit of hazard ratio (HR) = 1.5 (α-error = 0.075 one-sided significance level, β-error = 0.2 and 80% statistical power). A sample size of 152 patients was required. Considering a 10% drop-out rate, 168 patients were requested (84 patients in each arm, ratio 1 : 1). Randomization was carried out using a validated system that generated random assignment of treatment groups to randomization numbers.

Efficacy was evaluated in the intent-to-treat (ITT) population (i.e. all randomized patients) and per protocol (PP) population (all patients of the ITT population without major protocol deviations, who received the study treatment and had one or more post-baseline efficacy and/or safety assessment). The safety population included all randomized patients who received at least one dose of their assigned treatment.

The primary endpoint was PFS. Secondary endpoints included overall survival (OS), objective response rate (ORR), time to treatment failure (TTF), disease control rate (DCR), depth of response (DpR), detection of vulnerability using the Vulnerable Elders Survey (VES)-13 score,[17] and safety. A VES-13 score ≥3 was indicative of vulnerability. Safety was reported separately for the induction and maintenance phases. Exploratory analyses of factors influencing PFS or OS [including age range (70 versus >70-75 versus ≥75-80 versus ≥80 years), sex, baseline VES-13 score (≥3 versus <3), tumor location (right versus left site), *RAS* and *BRAF* mutational status, previous treatment (palliative) (EGFR versus bevacizumab versus others), first-line PFS (palliative treatment) (>9 months versus ≤9

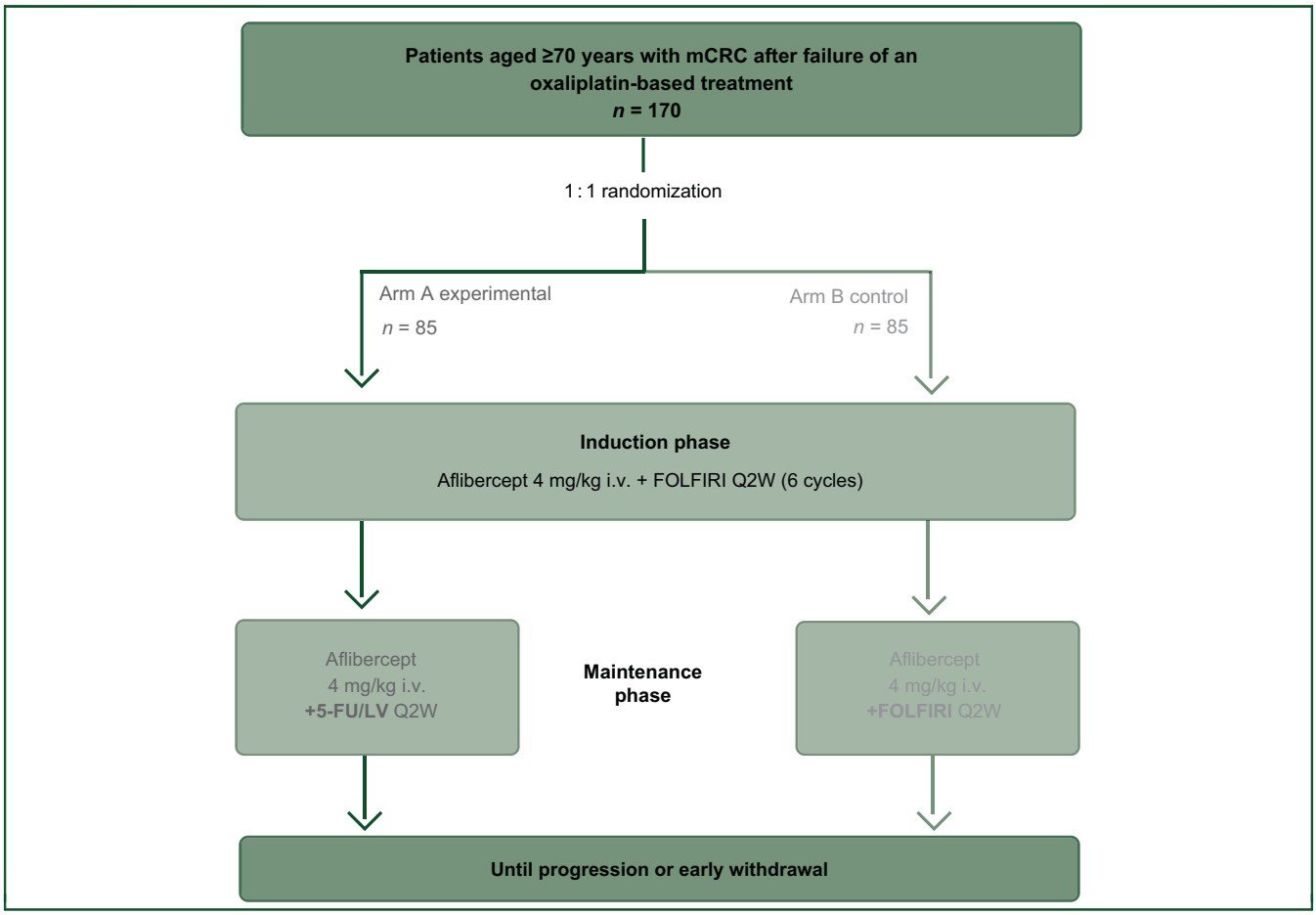

Figure 1. Study design. A total of 45 patients in arm A and 37 patients in arm B initiated the maintenance phase.
5-FU, 5-fluorouracil; LV, leucovorin; mCRC, metastatic colorectal cancer; Q2W, once every 2 weeks.

months), baseline neutrophil-to-lymphocyte ratio (NLR) (<5 versus ≥5), single versus multiple affected organs, liver metastasis (yes versus no), comorbidities (0 versus 1 versus 2), baseline lactate dehydrogenase (LDH) levels (normal versus high), and baseline carcinoembryonic antigen levels (<5 ng/ml versus ≥5 ng/ml)] were also conducted.

Survival curves were estimated using the Kaplan—Meier method and compared using the log-rank test. A Cox regression model was carried out to estimate HRs for the survival analysis. Comparisons of ORR, DCR, and VES-13 between groups were done using chi-square or Fisher test, as applicable. Comparisons of DpR between groups were carried out by the Mann—Whitney test. All statistical tests were two-sided, and P values < 0.05 were considered statistically significant. Statistical analyses were carried out using SPSS 22.0. software (SPSS Inc., Armonk, NY).

RESULTS

Of 204 patients assessed for eligibility, 34 patients were screening failures (mainly because eligibility criteria were not met). Thus, 170 patients were randomly allocated to FOLFIRI-A (six cycles) followed by 5-FU/LV-A ($n = 85$; arm A) or FOLFIRI-A ($n = 85$; arm B) until disease progression (Figure 2). Since all patients were exposed to treatment, the ITT population matched the safety population (Figure 2). Baseline characteristics were well balanced between the two arms (Table 1). The recruitment period was between 25 November 2017 and 11 February 2022. The date of last patient in the follow-up was 11 February 2023.

The most common reasons for treatment discontinuation were disease progression (arm A: 58.8% and arm B: 61.2%) and toxicity (arm A: 14.1% and arm B: 20.0%) (Figure 2). The median follow-up was 12.2 months (range 0.8-49.0 months) and 10.9 months (range 0.8-57.6 months) (arms A and B, respectively). Baseline characteristics of patients who did or did not achieve the maintenance phase are displayed in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103986.

All patients received three lines of treatment, 34.7% ($n = 17$) patients in arm A and 54.9% ($n = 28$) patients in arm B received four lines of treatment, 14.3% ($n = 7$) patients in arm A and 23.5% ($n = 12$) patients in arm B received five lines of treatment, 3 patients in each treatment arm received six lines of treatment, and 1 patient in arm B received seven and eight lines of treatment. Among patients with three lines of treatment, chemotherapy based on irinotecan was reported in 12.2% ($n = 6$) patients in arm A and 13.7% ($n = 7$) patients in arm B.

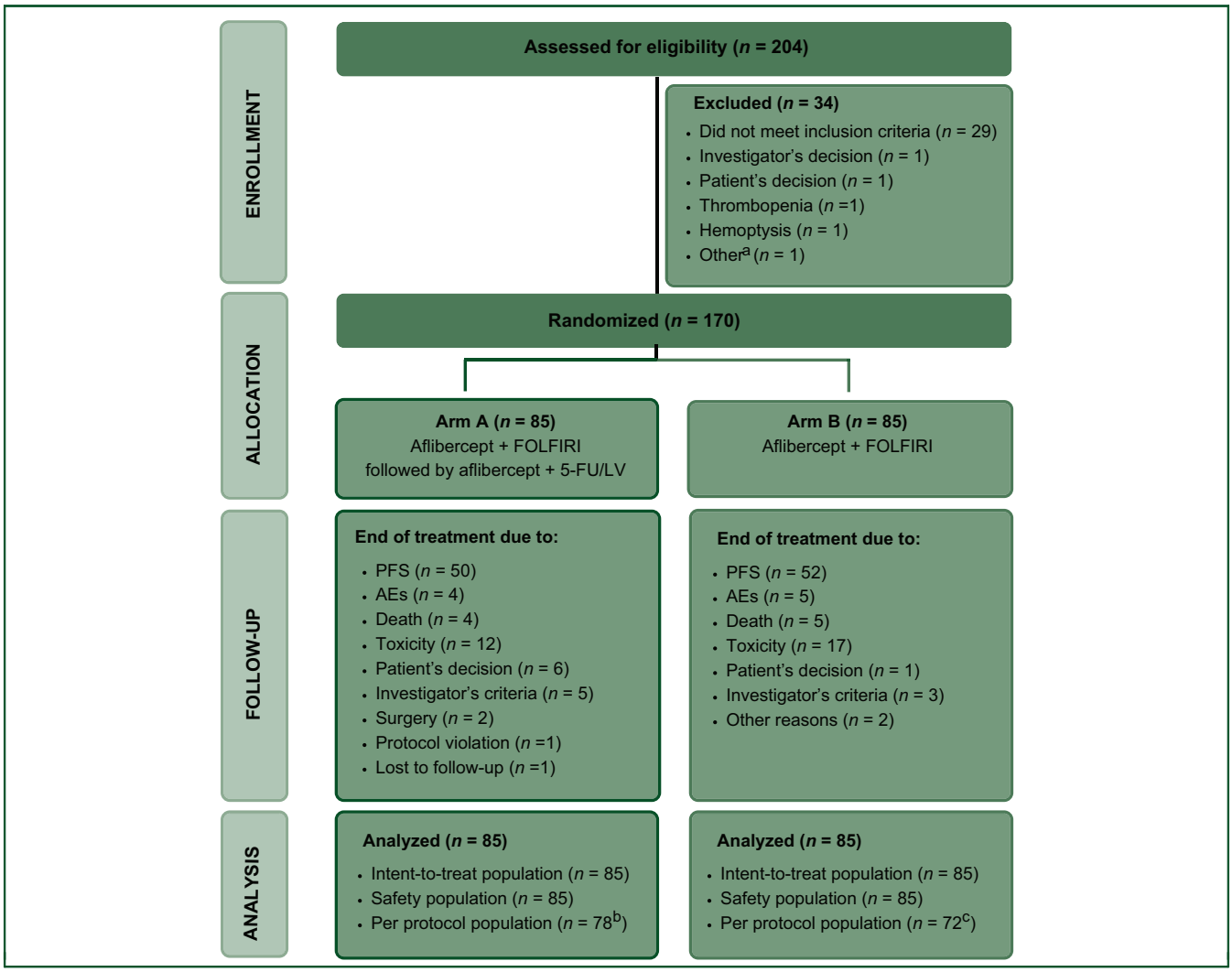

Figure 2. Patient flow chart.
5-FU, 5-fluorouracil; AE, adverse event; LV, leucovorin; PFS, progression-free survival; PP per protocol.
[a]Computerized tomography scan >35 days.
[b]Seven patients were excluded from the PP [in all of them the reason was that they did not have response evaluation criteria in solid tumors (RECIST) v1.1 assessment done before end of treatment].
[c]A total of 13 patients were excluded from the PP (12 patients did not have RECIST v1.1 assessment done before end of treatment and 1 patient had a protocol deviation 'previous tumor diagnosed <5 years ago'**).**

Efficacy

Primary endpoint. In the ITT population, the mPFS [95% confidence interval (CI)] was 6.1 months (5.3-6.9 months) and 5.5 months (4.8-6.2 months) in arms A and B ($P = 0.128$), respectively. Non-inferiority between the two arms (HR 0.781, 95% CI 0.566-1.076, $P = 0.131$) was met (Figure 3A). Similar results were observed in the PP population [6.4 months (5.7-7.2 months) and 5.6 months (5.0-6.3 months) in arms A and B ($P = 0.071$), HR 0.730, 95% CI 0.518-1.030, $P = 0.073$]. The PFS of patients who achieved the maintenance phase ($n = 82$) is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103986.

Secondary endpoints. A total of 71 (83.5%) and 75 (88.2%) patients died in arm A and arm B, respectively. Median OS (mOS) (95% CI) was 12.2 months (10.6-13.9 months) and 11.5 months (8.7-14.4 months) in arms A and B, respectively. No statistical difference between arms was observed (HR 0.886, 95% CI 0.640-1.227, $P = 0.467$) (Figure 3B). Median (95% CI) TTF was 5.6 months (4.2-6.9 months) and 4.0 months (2.5-5.5 months) in arms A and B, respectively (HR 0.750, 95% CI 0.551-1.021, $P = 0.068$) (Figure 3C). There was no statistical difference in ORR (20% versus 9.4%, $P = 0.082$), DCR (59% versus 47%, $P = 0.081$), and DpR (median 14.0 versus 4.1) in arm A versus arm B (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103986). Response measurements by induction and maintenance phase are described in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103986.

Factors influencing OS and PFS. A longer mPFS (95% CI) was observed in patients with an NLR at baseline <5 versus ≥5 [5.7 months (5.3-6.3 months) versus 4.6 months (2.7-6.6 months), $P = 0.008$] and those with single versus multiple

Table 1. Baseline demographics and disease characteristics of the study population

	Arm A $n = 85$	Arm B $n = 85$
Median age (range), years	74.0 (70.0-84.0)	73.0 (70.0-82.0)
Sex (male), *n* (%)	60 (70.6)	62 (72.9)
ECOG performance status, *n* (%)		
0	38 (44.7)	45 (52.9)
1	44 (51.8)	39 (45.9)
2	3 (3.5)	1 (1.2)
Primary tumor location[a], *n* (%)		
Right	32 (37.6)	26 (30.6)
Left	53 (62.4)	59 (69.4)
Liver metastases, *n* (%)	64 (75.3)	69 (81.2)
Metastatic sites, *n* (%)		
1	29 (34.1)	25 (29.4)
>1	56 (65.9)	60 (70.6)
Prior resection of primary tumor[b], *n* (%)	64 (75.3)	56 (65.9)
Mutations[c], *n* (%)		
KRAS[d]	41 (51.9)	52 (68.4)
RAS	6 (10.2)	10 (19.2)
BRAF	6 (10.7)	9 (19.1)
Prior OXA-FP-based chemotherapy, *n* (%)	85 (100)	85 (100)
OXA-FP alone	16 (18.8)	24 (28.2)
OXA-FP + anti-EGFR	20 (23.5)	11 (12.9)
OXA-FP + bevacizumab	47 (55.3)	49 (57.6)
Others	16 (18.8)	24 (28.2)
Prior radiotherapy	10 (11.8)	13 (15.3)
VES-13 score, mean (SD)[e]	3.1 (2.4)	2.5 (1.9)
<3, *n* (%)	33 (58.9)	34 (65.4)
≥3, *n* (%)	23 (41.1)	18 (34.6)

CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; OXA-FP, oxaliplatin-fluoropyrimidine; SD, standard deviation; VES-13, Vulnerable Elders Survey-13.
[a]Left location = left colon + rectum and right location = right colon + transverse colon.
[b]Any previous surgery (primary and/or metastasis) with radical or palliative resection.
[c]Molecular characterization was not available for the complete sample of patients: *KRAS* mutational status (exon 2/3) ($n = 155$), *RAS* (*NRAS* exon 2/3/4 and *KRAS* exon 4) ($n = 111$), *BRAF* ($n = 103$). *RAS* mutational status included *NRAS* exon 2/3/4 and *KRAS* exon 4.
[d]$P = 0.049$.
[e]Mean (SD) was calculated among a total of 56 patients in arm A and 52 patients in arm B that provided data of VES-13. VES-13 score ≥3 is indicative of vulnerability.

metastatic organs [7.6 months (6.0-9.1 months) versus 5.5 months (5.0-6.1 months), $P < 0.001$]. The VES-13 baseline score did not influence mPFS (5.8 versus 5.7 months in patients with VES-13 <3 versus ≥3, HR 1.147, 95% CI 0.760-1.730, $P = 0.511$). The mOS (95% CI) was longer in patients with left versus right tumors [12.4 months (10.4-14.4 months) versus 10.9 months (6.8-15.0 months), $P = 0.023$], single versus multiple metastatic organs [13.8 months (12.6-14.9 months) versus 10.9 months (8.3-13.5 months), $P = 0.010$], absence versus presence of liver metastases [13.8 months (8.8-18.8 months) versus 11.4 months (9.3-13.6 months), $P = 0.011$], and normal versus high LDH baseline levels [13.9 months (11.2-16.6 months) versus 9.4 months (7.2-11.6 months), $P < 0.001$]. Patients with VES-13 <3 versus VES-13 ≥3 tended to have a longer mOS (13.1 versus 10.9 months, HR 1.501, 95% CI 0.986-2.285, $P = 0.056$). No significant differences in the other variables analyzed were found.

Changes in VES-13 score during treatment. At baseline, 41.1% ($n = 23/56$) versus 34.6% ($n = 18/52$) of patients had a VES-13 score ≥3 in arm A versus arm B, respectively (Table 1), 45.2% ($n = 14/31$) versus 33.3% ($n = 11/33$) at cycle 6 of the induction phase, 40.7% ($n = 11/27$) versus 34.5% ($n = 10/29$) at cycle 1 of maintenance. No significant differences were observed in any case.

Safety

The median number of cycles administered was 6 (range 1-6) during the induction phase in both arms and 8 (range 1-30) in arm A and 7 (range 1-23) in arm B in the maintenance phase. The median time on treatment was 4.9 months (range 0.5-19.4 months) versus 3.1 months (range 0.5-14.9 months) in arms A and B, respectively. In arm A, 58.8% ($n = 50/85$) of patients completed the induction phase and 52.9% ($n = 45/85$) received the maintenance treatment. In arm B, 54.1% ($n = 46/85$) of patients completed the induction phase and 43.5% ($n = 37/85$) continued with FOLFIRI-A (maintenance phase). Only 3.5% of patients in both arms escalated dose level.

All patients experienced at least one AE. A total of 62 (72.9%) patients in arm A and 65 (76.5%) in arm B

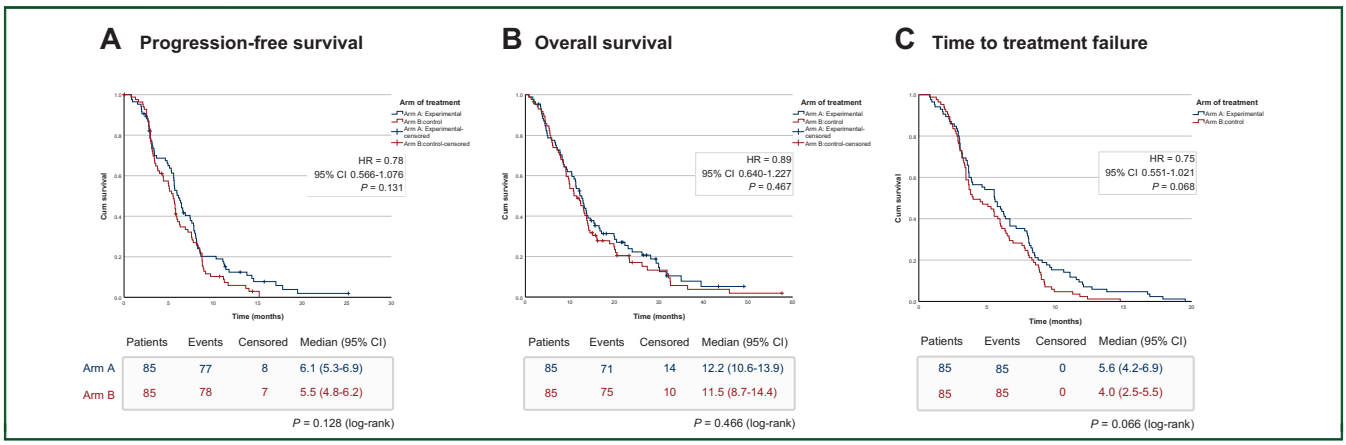

Figure 3. Progression-free survival and overall survival during the treatment with by arm A or arm B (ITT population). Arm A, FOLFIRI-aflibercept (six cycles) followed by maintenance treatment with 5-FU/LV-aflibercept; arm B, FOLFIRI-aflibercept.
5-FU, 5-fluorouracil; CI, confidence interval; Cumulative survival, Kaplan–Meier cumulative survival curve; HR, hazard ratio; LV, leucovorin; OS, overall survival; PFS, progression-free survival.

Table 2. Summary of adverse events

Adverse events, *n* (%)	Overall		Induction phase		Maintenance phase	
	Arm A ($n = 85$)	Arm B ($n = 85$)	Arm A ($n = 85$)	Arm B ($n = 85$)	Arm A ($n = 45$)	Arm B ($n = 37$)
AEs (related and non-related)						
Any grade	85 (100)	85 (100)	85 (100)	85 (100)	44 (97.8)	37 (100)
At least 1 AE Grade 1-2	82 (96.5)	84 (98.8)	82 (96.5)	84 (98.8)	42 (93.3)	36 (97.3)
At least 1 AE Grade ≥3	62 (72.9)	65 (76.5)	55 (64.7)	60 (70.6)	17 (37.8)	19 (51.4)
Grade 3-4 treatment-related AEs occurring in >5% of patients in either arm						
Asthenia	13 (15.3)	18 (21.2)	12 (14.1)	15 (17.6)	2 (4.4)	8 (21.6)[b]
Neutropenia	16 (18.8)	15 (17.6)	16 (18.8)	15 (17.6)	0 (0.0)	0 (0.0)
Diarrhea	9 (10.6)	9 (10.6)	8 (9.4)	8 (9.4)	2 (4.4)	3 (8.1)
Mucosal inflammation	9 (10.6)	6 (7.1)	9 (10.6)	5 (5.9)	1 (2.2)	1 (2.7)
Hypertension	7 (8.2)	5 (5.9)	5 (5.9)	5 (5.9)	4 (8.9)	0 (0.0)
Decreased appetite	2 (2.4)	5 (5.9)	2 (2.4)	4 (4.7)	0 (0.0)	2 (5.4)
SAEs[a]	35 (41.2)	37 (43.5)	30 (35.3)	28 (32.9)	8 (17.8)	14 (37.8)[c]
Treatment-related SAEs	21 (24.7)	16 (18.8)	20 (23.5)	13 (15.3)	3 (6.7)	4 (10.8)
AEs leading to death	6 (7.1)	12 (14.1)	5 (5.6)	8 (9.4)	1 (2.2)	4 (10.8)[a]
Treatment-related AEs leading to death						
Intestinal ischemia	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)
Intestinal perforation	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Sepsis	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)

AE; adverse event; SAE, serious adverse event.
[a]SAEs occurring in >4% of patients were diarrhea [8.2% ($n = 7$) in both arms], intestinal obstruction [2.4% ($n = 2$) in arm A versus 8.2% ($n = 7$) in arm B] and urinary tract infection [4.7% ($n = 4$) in arm A versus 1.2% ($n = 1$) in arm B]. Significant differences between treatment arms in the maintenance phase with
[b]$P = 0.037$.
[c]$P = 0.049$ and [d]$P = 0.038$, respectively (Fisher test, in all three cases).

presented at least one grade ≥3 AE, mainly asthenia [arm A versus B: 15.3% ($n = 13$) versus 21.2% ($n = 18$)] and neutropenia [18.8% ($n = 16$) versus 17.6% ($n = 15$)] (Table 2).

There were no statistically significant differences in grade 3-5 toxicities according to VES-13 score (76.1% for VES-13 <3 versus 70.7% for VES-13 ≥3).

The percentage of patients experiencing serious AEs (SAEs) was similar in arm A versus arm B: 41.2% ($n = 35$) versus 43.5% ($n = 37$), and the most common SAEs were diarrhea [arm A versus arm B: 9.4% ($n = 8$) versus 8.2% ($n = 7$)] and intestinal obstruction [arm B versus arm A: 8.2% ($n = 7$) versus 1.2% ($n = 1$)]. In the maintenance phase, however, SAEs were experienced by a significantly lower percentage of patients in arm A versus arm B [17.8% ($n = 8$) versus 37.8% ($n = 14$), $P = 0.049$], with a numerically lower percentage of patients reporting treatment-related SAEs [arm A versus arm B: 6.7% ($n = 3$) versus 10.8% ($n = 4$), $P = 0.695$] and a reduced incidence of patients with grade 3-4 AEs [mainly asthenia, arm A versus arm B: 4.4% ($n = 2$) versus 21.6% ($n = 8$), $P = 0.037$] (Table 2).

The dose of FOLFIRI was reduced due to unacceptable grade ≥3 toxicity [mainly neutropenia (31.4%), asthenia (28.6%), and mucosal inflammation (17.1%)] which led to death in two patients (5.7%, 2/35). After this amendment, 2 out of 135 patients (1 patient in each arm) (1.5%) died due to intestinal ischemia in arm A and intestinal perforation in arm B. In addition, there was a statistically significant reduction in asthenia, neutropenia, and mucositis during the induction phase after the amendment (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103986).

A total of 6 (7.1%) and 12 (14.1%) patients in arms A and B, respectively, had fatal AEs (2 of them in each arm were reported before the amendment, see Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103986). Fatal AEs considered as treatment related were reported in two patients (2.4%) in arm A [sepsis (before amendment) and intestinal ischemia (after amendment)] and two patients (2.4%) in arm B [intestinal ischemia (before amendment) and intestinal perforation (after amendment)].

DISCUSSION

Results of the AFEMA study are important for two reasons. Firstly, to our knowledge this is the first randomized study that assesses maintenance treatment in a second-line setting. Secondly, it included patients ≥70 years of age (some of whom are at high risk of vulnerability) who are underrepresented in clinical trials. The primary endpoint was met: six cycles of FOLFIRI-A followed by maintenance with 5-FU/LV-A was non-inferior to FOLFIRI-A until progression in terms of PFS. Secondary endpoints were similar between arms. Of note, the significant higher frequency of *KRAS* mutations in the control arm versus the experimental arm could have contributed to the slightly inferior PFS, OS and/or response rates in the control arm. More importantly, the number of patients experiencing SAEs, severe asthenia, and treatment-related SAEs were reduced in the maintenance arm with 5-FU/LV-A.

The AFEMA protocol was amended after 35 patients were included to reduce the dose of FOLFIRI to level 1 due to unacceptable toxicity. Importantly, this amendment reduced the percentage of patients experiencing AEs leading to death from 5.7% to 1.5% and allowed completion of study recruitment. This chemotherapy dose reduction and switch to maintenance with aflibercept and 5-FU after six

cycles was associated with an mPFS of 6.1 months, an mOS of 12.2 months, an ORR of 20%, and a DCR of 69.4%. Such results compare nicely with the VELOUR phase III trial (median age 61 years) without major comorbidities, which showed that aflibercept + FOLFIRI until progression resulted in an mPFS of 6.9 months, an mOS of 13.5 months, an ORR of 19.8%, and a DCR of 74.3%.[13] In the NORDIC-9 study,[18] a reduced-dose combination chemotherapy with S-1 and oxaliplatin had a significantly longer PFS (6.2 versus 5.3 months), a trend to a longer OS (14.5 versus 11.5 months), and resulted in less toxicity compared with a full-dose monotherapy with S1 in older, more vulnerable adults with untreated mCRC. In the FOCUS-2 study which evaluated a reduced-dose combination therapy (80% oxaliplatin with capecitabine or 5-FU) versus a reduced-dose monotherapy (80% capecitabine or 5-FU) in mCRC patients unfit to receive a full-dose combination chemotherapy, there was a trend towards a longer PFS in the combination arm (5.8 versus 3.5 months).[19] Since there is increasing evidence that combination therapy is more effective than monotherapy in older adults with mCRC, reducing chemotherapy to level 1 and switching to maintenance after six cycles is, therefore, an interesting option to balance efficacy and safety in this difficult-to-treat population.

In the AFEMA study, right-sided tumor location, multiple affected organs, liver metastasis, high LDH levels, and NLR at baseline $\geq$5 were associated with a worse prognosis. A retrospective evaluation showed that stage IV at diagnosis and right-sided tumors were associated with a shorter PFS and OS.[20] Different prognostic models were developed,[21,22] but the NLR was not incorporated in any of these. A systematic review, however, concluded that high NLR was associated with poor OS in many non-metastatic and metastatic solid tumors, including CRC.[23]

In terms of toxicity, doublet chemotherapies combined with targeted agents tend to increase toxicity in older adults.[24] In our study, the toxicity profiles of both treatment arms were similar, but the maintenance approach significantly reduced the rate of grade 3-4 asthenia which may have a positive impact on quality-of-life. An age-based analysis comparison (phase III trial VELOUR) reported that patients aged $\geq$65 years receiving FOLFIRI-A displayed a numerically higher frequency of asthenia (grade 3-4) versus younger ones (14.8% versus 21.0%).[14] In an observational study in patients treated with FOLFIRI-A (19% aged $\geq$70 years), the most frequent grade 3-4 AEs of all ages combined was asthenia (21.3%), comparable to the AFEMA study (21.3%); the comparison by subgroups confirmed that patients aged $\geq$75 years had a significantly higher frequency of grade 3-4 asthenia versus those aged 70-74 years (36.0% versus 14.0%, $P = 0.038$).[25]

Several tools assessing vulnerability in cancer patients have been developed.[26,27] In the present study, VES-13 was used to identify patients at high risk of vulnerability. A total of 38% patients were identified as vulnerable at baseline. Interestingly, there was no difference in severe toxicities in patients with a VES-13 score $\geq$3 versus <3. This supports findings that FOLFIRI-A maintains quality-of-life in older adults.[28,29]

Further studies outside of the limitations of a phase II study should be carried out to confirm these results in the current study. Another study limitation is the lack of a specific quality-of-life assessment, especially in this older population. Future research should be focused on improving treatment in older adults who are usually more vulnerable and experience higher rates of AEs.

CONCLUSIONS

In conclusion, induction with six cycles of FOLFIRI-A followed by maintenance with 5-FU/LV-A was non-inferior to FOLFIRI-A until progression in older adults aged $\geq$70 years with mCRC. The reduced dose (level 1) would be the recommended dose for this population. Severe asthenia, SAEs, and treatment-related SAEs were reduced during the maintenance phase compared with the control arm. The AFEMA study shows that maintenance with the 5-FU/LV-A regimen represents an interesting treatment option for older adults with mCRC treated with FOLFIRI-A in a second-line setting.

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DISCLOSURE

PGA is speaker bureau for Amgen, Roche, Merck-Serono, Sanofi-Aventis, Pierre Fabre, and Servier; has done advisory activities from Amgen, Roche, Merck-Serono, Sanofi-Aventis, Pierre Fabre, and Servier; has received travel, accommodations and expenses from Amgen, Roche, Merck-Serono, Sanofi-Aventis, Pierre Fabre, and Servier. EE has received honoraria for consulting, lectures and/or speakers bureaus and/or travel from Amgen, Bayer, Cure Teq, AG Hoffmann-La Roche, Bristol Myers Squibb (BMS), Boehringer Ingelheim, Janssen, Lilly, Medscape, Merck Serono, Merck Sharp & Dohme (MSD), Novartis, Organon, Pfizer, Pierre Fabre, Repare Therapeutics Inc., RIN Institute Inc., Sanofi, Seagen, Servier, and Takeda; has participated on data safety monitoring boards or advisory boards from Amgen, Bayer, Cure Teq, AG Hoffmann-La Roche, BMS, Boehringer Ingelheim, Janssen, Lilly, Medscape, Merck Serono, MSD, Novartis, Organon, Pfizer, Pierre Fabre, Repare Therapeutics Inc., RIN Institute Inc., Sanofi, Seagen, Servier, and Takeda. JSA has received honoraria from Merck, Ipsen, Pfizer, Recordati, Servier, and Leo Pharma; has

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DATA SHARING

Data related to this study are available upon reasonable request from the corresponding author.

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