Abstract 3555 Aflibercept-LV5FU2 as first-line treatment of non-resectable metastatic colorectal cancers: Results of the FOLFA randomized phase II trial.

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PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

Background

- Previous tirals : efficacy and safety of fluoropyrimidine and bevacizumab combination in metastatic colorectal cancer

Landre T et al Int J Colorectal Dis 2018

- Especially in older patients
- **PRODIGE 25 – FOLFA** :
  - Randomized, non-comparative phase II trial
  - Efficacy and safety of **aflibercept** associated with **LV5FU2s regimen** in patients with metastatic, non-resectable/non operable colorectal cancer
  - Patients non eligible for front-line doublet chemotherapy with irinotecan and/or oxaliplatin

Patients and methods

- Main eligibility criteria
  - Age ≥ 65 ans
  - WHO performance status <2
  - Non-resectable disease or non-operable patient
  - Patient non eligible (local staff) for a combination chemotherapy with irinotecan or oxaliplatin
  - Not symptomatic or little symptomatic metastases and at least one measurable lesion (RECIST V1.1)
  - Non previous treatment of the metastatic disease. Possible adjuvant chemotherapy completed at least 6 months ago
- Main exclusion criteria
  - **Symptomatic primary tumor** (obstruction, haemorrhage)
  - Dihydropyrimide dehydrogenase deficiency
  - **Uncontrolled hypertension** (systolic blood pressure >150 mm Hg and/or diastolic blood pressure >100 mm Hg)
  - **Cardio-vascular damages in the 6 months before inclusion:** myocardial infarction, severe/unstable angina, coronary artery bypass surgery, congestive heart failure class NYHA III or IV, stroke or transient ischemic attack, pulmonary embolism. Taking oral anticoagulant (except anti-vitamin K)
  - **Digestive damages in the 3 months before inclusion:** grade 3 or 4 gastro-intestinal bleeding, treatment-resistant peptic ulcer, oesophagitis or ulcerative gastritis, infectious or inflammatory intestinal disease, diverticulitis.

Stratification

- Center
- *Thymidylate synthase (TS) 5'UTR* gene polymorphism (centralized determination) : 3R3R *vs* 2R2R or 2R3R. Pronostic biomarker, predictive biomarker of the efficacy of 5FU ? FFCD 2001-05. V Boige et al, JCO 2010
- Age (≤ 75 years *vs* >75 years)
- Number of metastatic site: 1 *vs* >1

Primary endpoint: 6-month progression-free survival (PFS) rate, achieved if > 40% in the experimental arm. (patients alive and without progression according to investigator)

Secondary endpoints: toxicity, Quality of live (EORTC QLQC30 and time to definitive deterioration of quality of live), 1- and 3-year overall survival, impact of the *TS polymorphisme 5'UTR* polymorphism on the survival

R

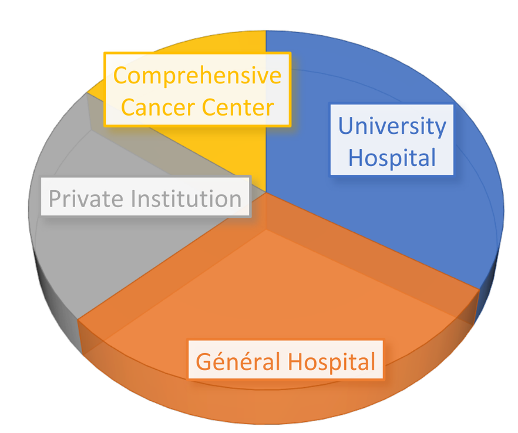
Experimental arm: A
Aflibercept (4mg/kg) + **LV5FU2s** / 14 j
Until progression or unacceptable toxicity

Reference arm: B
LV5FU2s / 14 j Until progression or unacceptable toxicity

Population

- 117 patients (pts) included. 61.5% male
- Median age 81 years (ranges 67-91). 81 % pts age > 75 years
- Mutated *RAS* status: 49%
- Mutated *BRAF* status: 7%

CARE INSTITUTION

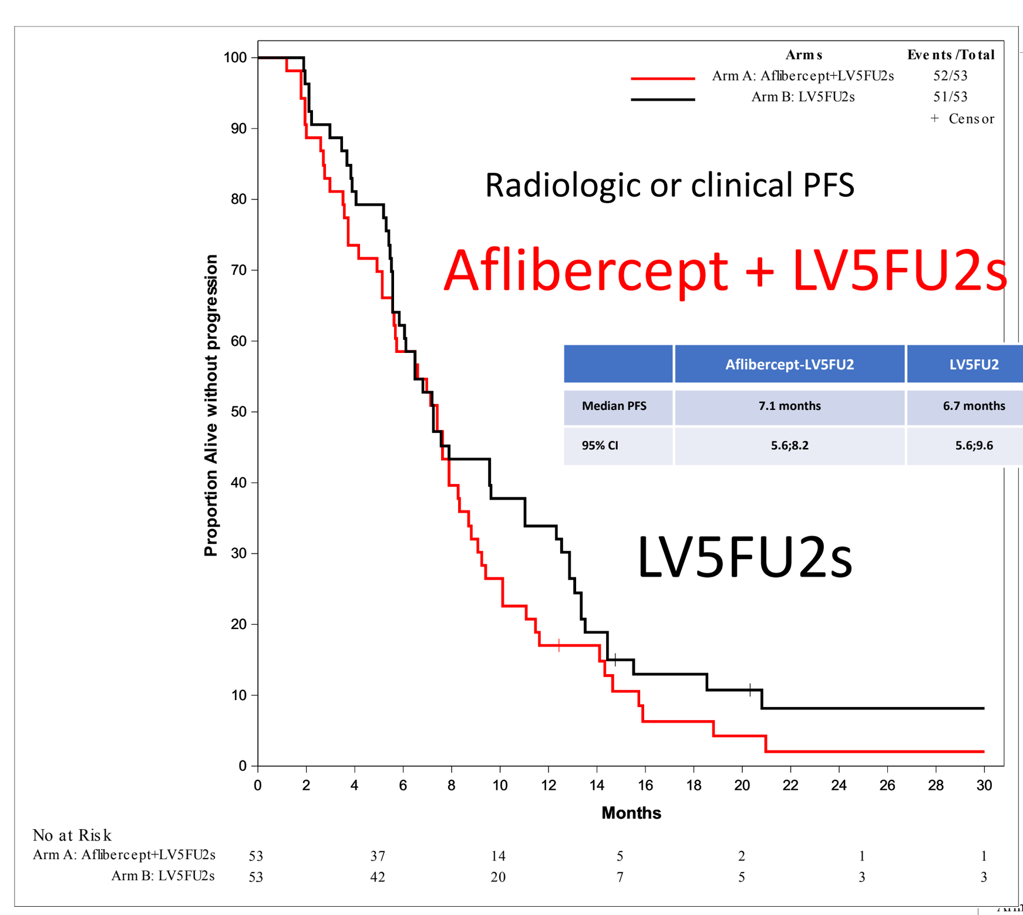


		Arm A : Aflibercept + LV5FU2s	Arm B : LV5FU2s	Total	P-value
		(N=56)	(N=56)	(N=112)	
Age	≤ 75 years	13 (22.0%)	9 (15.5%)	22 (18.8%)	
	> 75 years	46 (78.0%)	49 (84.5%)	95 (81.2%)	
Number of metastatic sites	1	23 (39.0%)	26 (44.8%)	49 (41.9%)	
	>1	36 (61.0%)	32 (55.2%)	68 (58.1%)	
TS polymorphism	*2R2R-2R3R*	45 (76.3%)	44 (75.9%)	89 (76.1%)	
	3R3R	14 (23.7%)	14 (24.1%)	28 (23.9%)	
WHO Performance status	0	14 (25.0%)	23 (41.1%)	37 (33.0%)	0.0706
	1	42 (75.0%)	33 (58.9%)	75 (67.0%)	
Systolic blood pressure (mmHg)	median	139.00	134.50	136.50	
Diastolic blood pressure (mmHg)	median	70.00	74.50	73.00	
Köhne score	low	22 (39.3%)	25 (44.6%)	47 (42.0%)	0.0885
	middle	27 (48.2%)	30 (53.6%)	57 (50.9%)	
	high	7 (12.5%)	1 (1.8%)	8 (7.1%)	
Creatinin clearance (ml/min)	median	65.00	67.50	66.50	
Alkaline Phosphatases (UI/L)	median	123.00	100.50	107.00	**0.002**
GGT (UI/L)	median	93.50	64.00	84.00	**0.004**

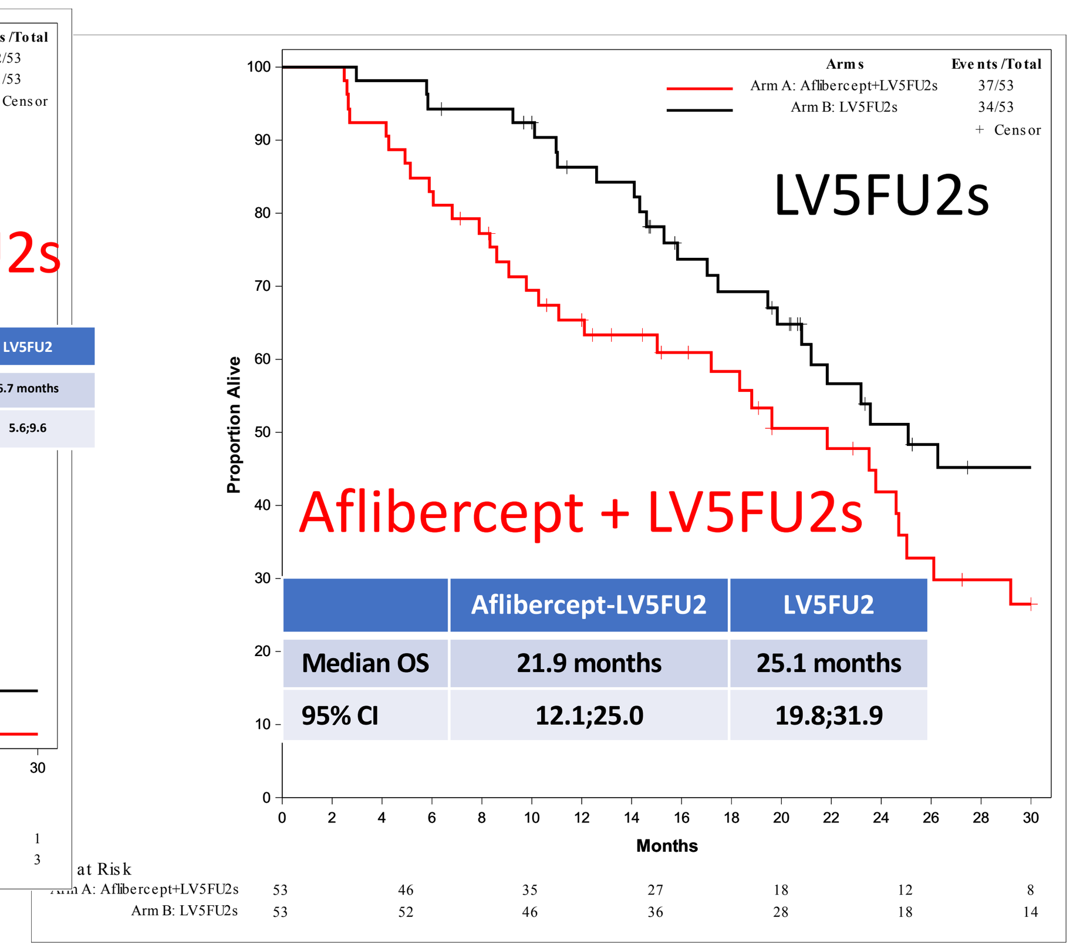
Results

	Aflibercept-LV5FU2	LV5FU2	
PFS at 6 months Patient alive and without progression	53.6 % 90% CI: 41.8;65.1	53.6 % 90% CI: 41.8;65.1	> 40 % pts
Radiologic PFS at 6 months Patient alive and without radiologic progression	median **7.3 months** 95% CI: 5.6;8.2	median **7.2 months** 95% CI: 5.6;9.6	
Complete/partial response	0 % / 26.4 %	0 % / 40 %	
Disease control	83%	87%	

Progression Free Survival



Overall Survival



Toxicity

	Aflibercept-LV5FU2	LV5FU2
Grade 3-4 toxicities	82%	58%
Grade 3-4 high blood pressure	42%	18%
Proteinuria (all grade)	51%	11%
Dysphonia (all grade)	19%	2%
Grade 1-2 haemorrhage	5,3%	2%
Grade 3-4-5 haemorrhage	3,5%	0%

1 colic perforation in the arm Aflibercept

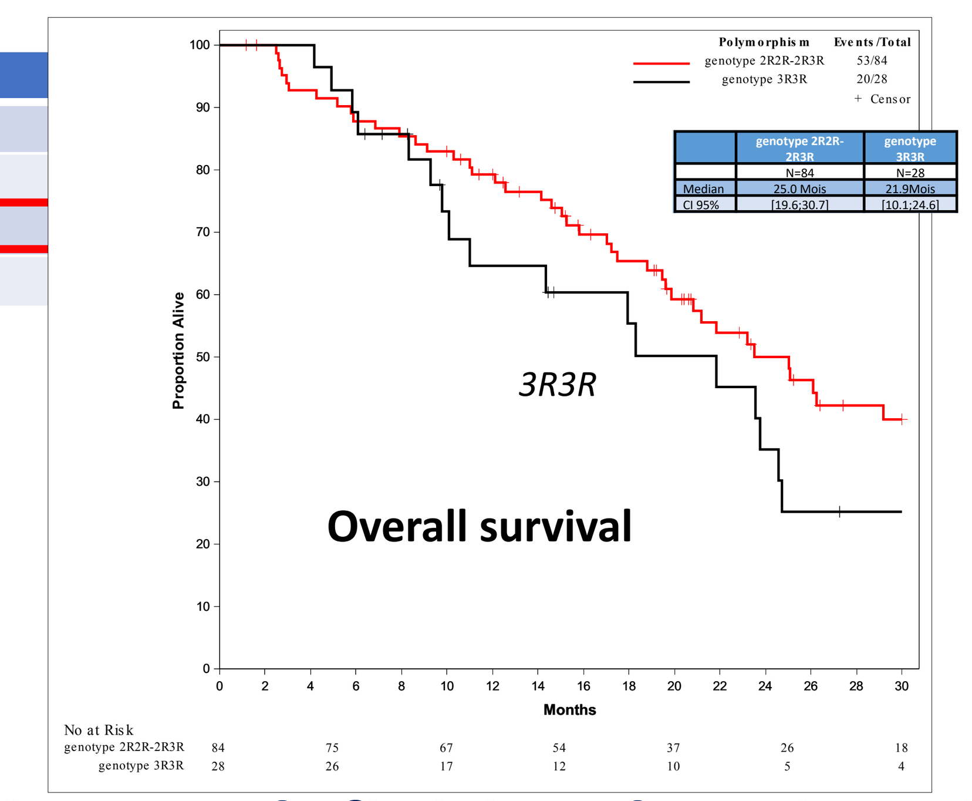
% theorical dose: mean (standard deviation)

	Aflibercept + LV5FU2s	LV5FU2s
Aflibercept	73.2 (32.2)	
5FU bolus and infusional	91.0 (12.1)	94.8 (9.3)
- 5FU: bolus	78.5 (32.0)	83.5 (31.0)
- 5FU: infusional	93.1 (10.5)	96.7 (7.1)

Cycles delayed for toxicity

	Aflibercept + LV5FU2s	LV5FU2s
Delay in treatment per patient	42 (73.7%)	40 (72.7%)
Delay in treatment due to toxicity /total delayed cycles	**25 %**	**14 %**
Cycles delayed for toxicity / number of cycles	4.3 %	1.8 %

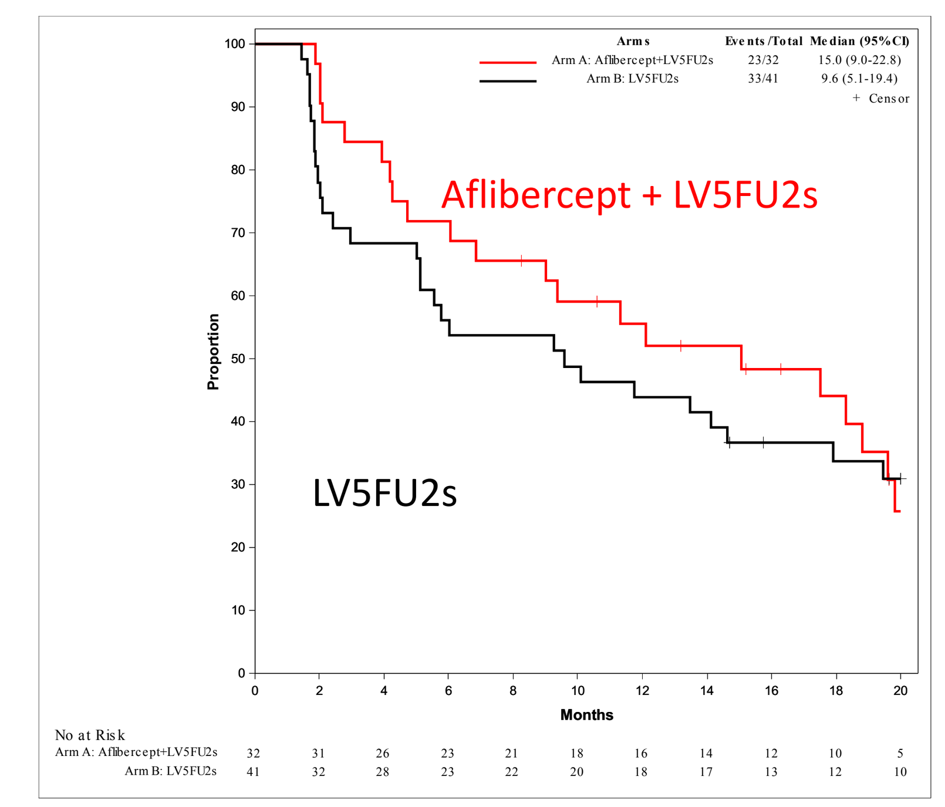
Thymidilate Synthase 5'UTR gene polymorphism: *3R3R vs 2R2R or 2R3R*



Subsequent treatments

	Aflibercept + LV5FU2s	LV5FU2s
Further ligne 2	40.3 %	70.9 %
Further ligne 3	26.3 %	47.3%

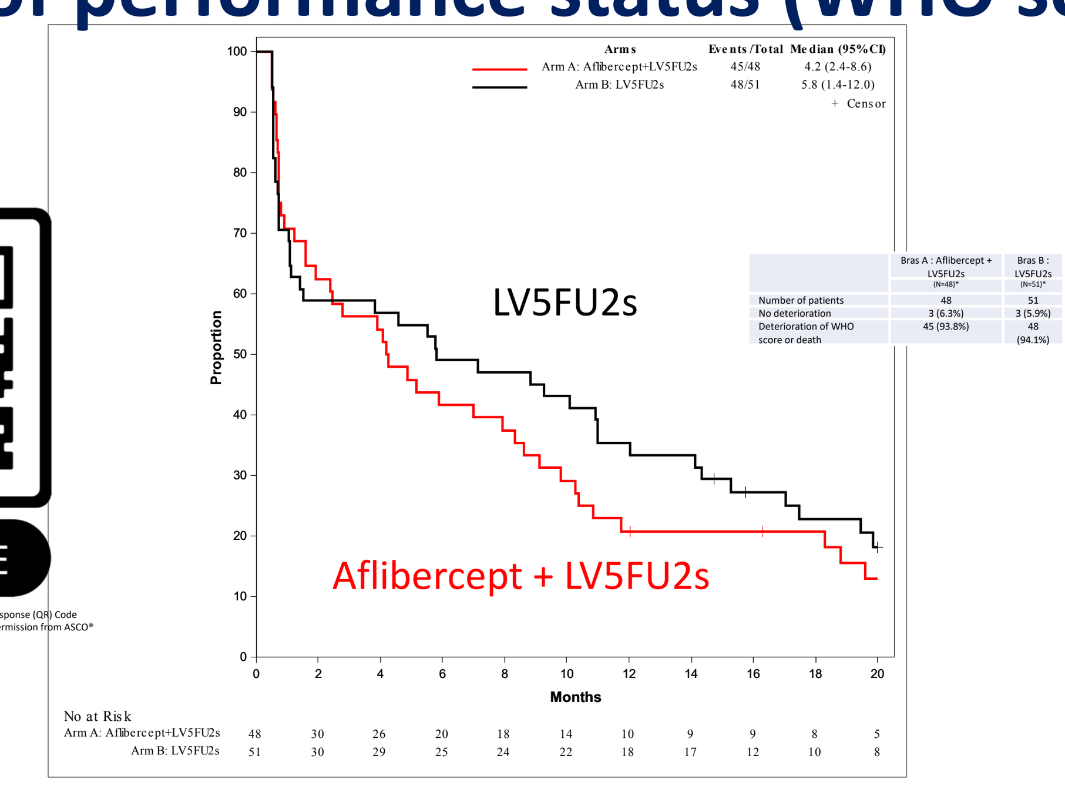
Quality of life (QLQ-C30)



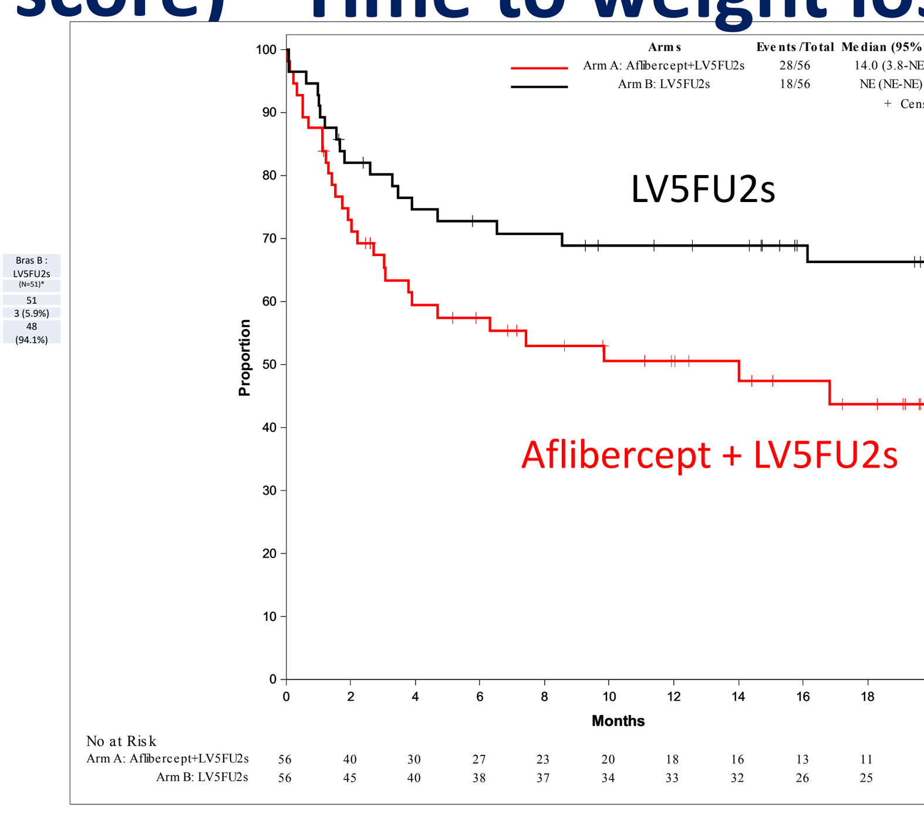
3 dimensions better in arm A
- Physical functioning,
- emotions,
- loss of appetite

Global score : Time to definitive deterioration

Time to definitive deterioration of performance status (WHO score)



Time to weight loss > 5%



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Discussion

Trial	Arms compared	N	Objective responses	PFS	OS
VELOUR (Line 2)	FOLFIRI/aflibercept FOLFIRI	612 614	20% 11%	6.9 p<0.0001 4.7 HR 0.76 (0.66-0.87)	13.5 p =0 .0032 12.06 HR 0.82 (0.71-0.94)
VELOUR (Line 2) Pts ≥ 65 years	FOLFIRI/aflibercept FOLFIRI	20 5 23 8		6.6 4.4 HR 0.75 (0.48-1.17)	12.6 11.3 HR 0.80 (0.68-1.07)
PRODIGE 25-FOLFA Line 1 (Pts ≥ 65 ans)	LV5FU2s/aflibercept LV5FU2s	59 58	26.4% 40%	7.1 6.7	21.8 25.1
AFFIRM Line 1	mFOLFOX6/aflibercept mFOLFOX6	11 9 11 6	49% 46%	8.5 8.8 HR 1.00 (0.74-1.36)	19.5 22.3

Conclusion

Our results do not support a subsequent randomized phase III trial evaluating first-line fluoropyrimidine with aflibercept vs fluoropyrimidine alone in metastatic colorectal patientts

Aknowledgments : patients and caregivers, FFCD, SANOFI