GASTRO JournalClub

L'importanza della ricerca in Oncologia

10-11 OTTOBRE 2019 - ROMA

VOI Donna Camilla Savelli Hotel - Via Garibaldi, 27

LA RICERCA CLINICA IN ITALIA E IN EUROPA: STUDI IN CORSO

FONDAZIONE GISCAD

GISCAD: DISTINCTIVE

(seconD-line folfiri aflIbercept in proSpecTIvely stratified, anti-EGFR resistaNt, metastatic coloreCTal cancer patients with RAS validated wild type status)

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STRATEGIC DECISION IN II LINE METASTATIC COLORECTAL CANCER

ESMO consensus guidelines for the management

Table 4. Drivers for first-line treatment

Tumour characteristics	Patient characteristics	Treatment characteristics
Clinical presentation: Tumour burden Tumour localisation	Age	Toxicity profile
Tumour biology	Performance status	Flexibility of treatment administration
RAS mutation status	Organ function	Socioeconomic factors
BRAF mutation status	Comorbidities, patient attitude, expectation and preference	Quality of life

Previous treatments related factors		
Which chemo	Which biologic	Which response
Tolerance	Residual toxicities	Drug free-interval

Van Cutsem E et Al, Ann Oncol 2016 & ESMO GI 2017

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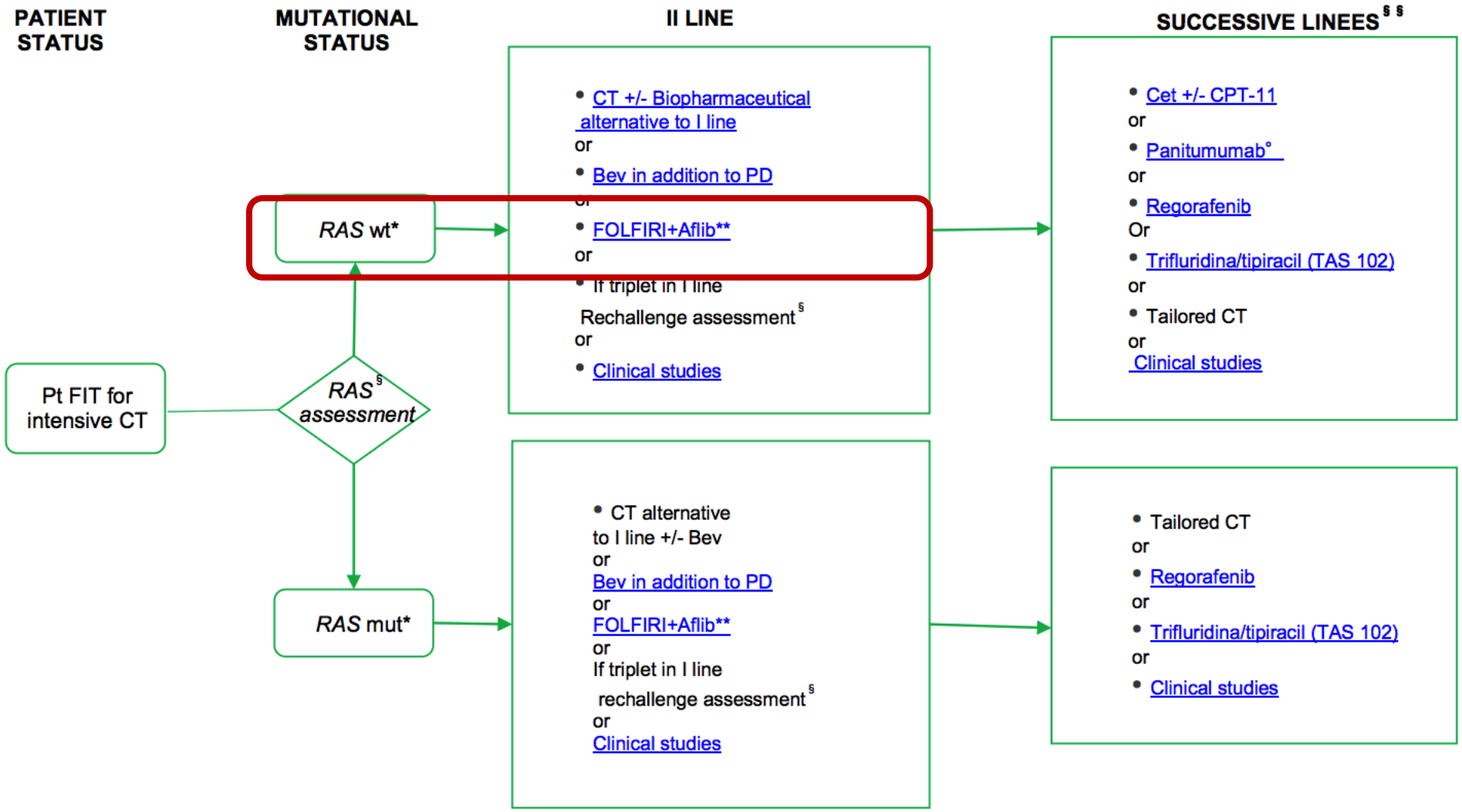
STRATEGIC DECISION IN II LINE METASTATIC COLORECTAL CANCER



Linee Guida AIOM 2018

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Angiogenesis inhibition in second line

	Bevacizumab		Aflibercept	Ramucirumab
Study	**TML**	**E3200**	**VELOUR**	**RAISE**
	100% prior beva	No prior beva	30% prior beva	100 % prior beva
mOS	11.2 vs 9.8	12.9 vs 10.8	13.5 vs 12.1	13.3 vs 11.7
HR	0.81*	0.75*	0.82*	0.84*
mPFS	5.7 vs 4.1	7.3 vs 4.7	6.9 vs 4.7	5.7 vs 4.5
HR	0.68*	0.61*	0.76*	0.79*
RR (%)	5.4 vs 3.9	22.7* vs 8.6	19.8* vs 11.1	13.4 vs 12.5

***p<0.05**

Bennouna Lancet Oncol 2012 – Giantonio JCO 2007 – Van Cutsem JCO 2012 – Tabernero Lancet Oncol 2015

VELOUR study

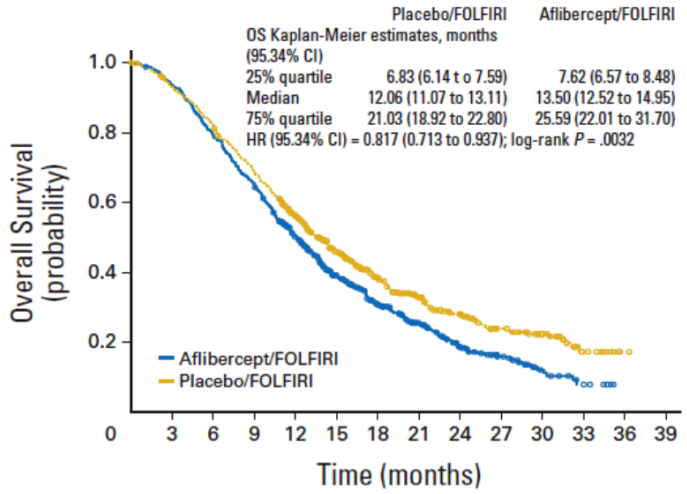
Patients with mCRC who progressed after 1L oxaliplatin and fluoropyrimidine ±bev

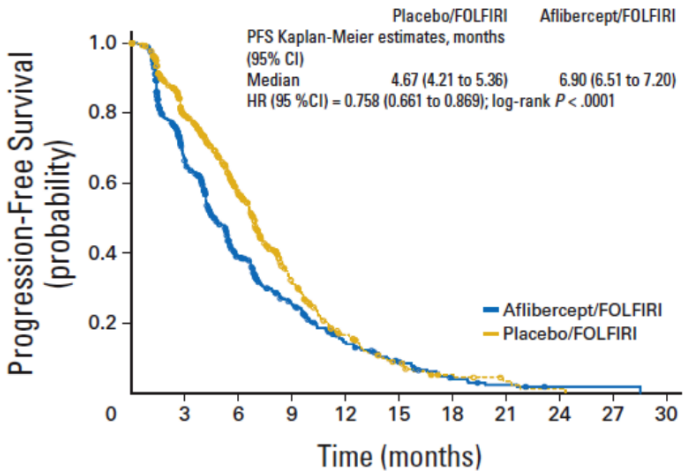
(n=1,226)

R

Aflibercept + FOLFIRI (n=612) → PD

Placebo + FOLFIRI (n=614) → PD

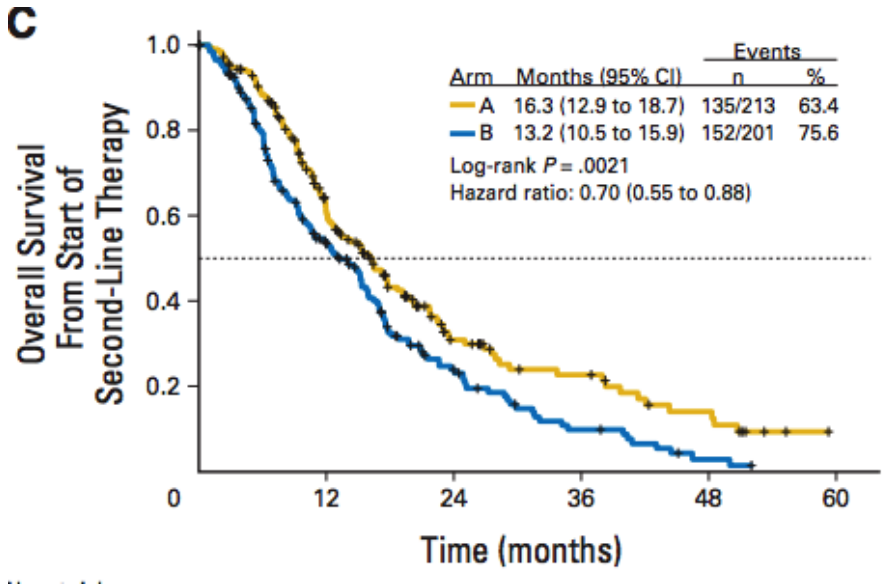


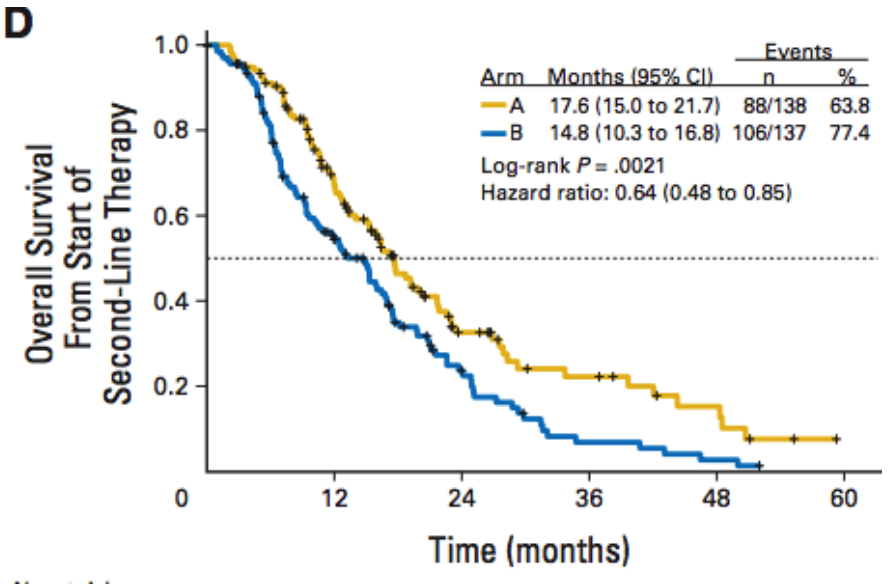


Van Cutsem E, et al. J ClinOncol2012;30(28):3499–506

Angiogenesis inhibition in second line after anti EGFR

Impact of Subsequent Therapies on Outcome of the FIRE-3/AIO KRK0306 Trial: First-Line Therapy With FOLFIRI Plus Cetuximab or Bevacizumab in Patients With *KRAS* Wild-Type Tumors in Metastatic Colorectal Cancer





Agent/Intervention	*KRAS* Exon 2 Wild Type No. (%)		*RAS* Wild Type No. (%)	
	FOLFIRI + Cetuximab (n = 297)	FOLFIRI + Bevacizumab (n = 295)	FOLFIRI + Cetuximab (n = 199)	FOLFIRI + Bevacizumab (n = 201)
Second-line therapy				
Fluoropyrimidines	200 (67.3)	170 (57.6)	128 (64.3)	117 (58.2)
Irinotecan	36 (12.1)	35 (11.9)	27 (13.6)	17 (8.5)
Oxaliplatin	139 (46.8)	126 (42.7)	89 (44.7)	90 (44.8)
Cetuximab/panitumumab	34 (11.4)	89 (30.2)	27 (13.6)	54 (26.9)
Bevacizumab	102 (34.3)	33 (11.2)	60 (30.2)	22 (10.9)
Exclusive others	2 (0.6)	4 (1.4)	1 (0.5)	4 (2.0)

Modest et Al JCO 2015

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Potential predictive biomarkers

Biomarkers	Technique for monitoring angiogenesis	Examples	Comments
Molecular			
Circulating angiogenic factors	ELISA, WB, proteomics, Luminex Multiplex or FACS array technologies	VEGF; FGF-2; MMP-9; IL-8; IL-6; HGF	Prognostic value in many cancers
EC-derived molecules	ELISA, WB, proteomics, antibodies arrays	sVEGFR1, sVEGFR2, sVEGFR3; sTie-2, VCAM-1	Limited to 'known' molecules
Circulating proteins or peptides	ELISA, WB, proteomics, antibodies arrays	Endostatin; tumstatin	Promising approach to identify novel molecules in serum or tumor tissues
Signaling events	Immunohistochemistry, Immunofluorescence	Phospho-Erk; Phospho-Akt	Limited feasibility in clinical practice
Biological			
Microvascular density Endothelial cell proliferation/death	Immunohistochemistry, Immunofluorescence	$CD31^+$, $CD34^+$, $VEGFR2^+$, $CD105^+$ vessels Ki67/CD31; Tunel/CD31	Prognostic value in many cancers Limited feasibility in clinical practice
CEC or CECP	Flow cytometry, Veridex technology	EC: $CD45^-$; $CD31^+$, $CD146^+$, $CD144^+$; $VEGFR2^+$ CECP: CD133 $CD34^+$; $CD144^+$; $VEGFR2^+$	Promising approach. Nonstandardized protocols. Labor intensive
Functional			
Functional imaging	DCE-MRI DCE-CT PET Power (color) Doppler (ultrasound) Contrast-enhanced ultrasound	Gadolinium chelate tracers Iodine-based tracers $H_2{}^{15}O$ tracer Microbubbles (Sonovue®, Bracco Diagnostics Inc., Plainsboro, NJ)	Allows measurement of MTT, rBF, rBV, pO_2, pH, and vascular permeability. Evidence of modification by therapy. Used in many studies, but no standard protocols available yet. Inexpensive, easy and safe techniques to monitor blood flow Allows quantitative measurement of blood flow
Molecular imaging	Tracer coupled to mAb or peptide against a vascular target, detected by PET or ultrasound	Targeting EDB+-fibronectin Targeting αVβ3 integrin	May improve specificity and sensitivity of functional vascular imaging. Complementary to dynamic measurements

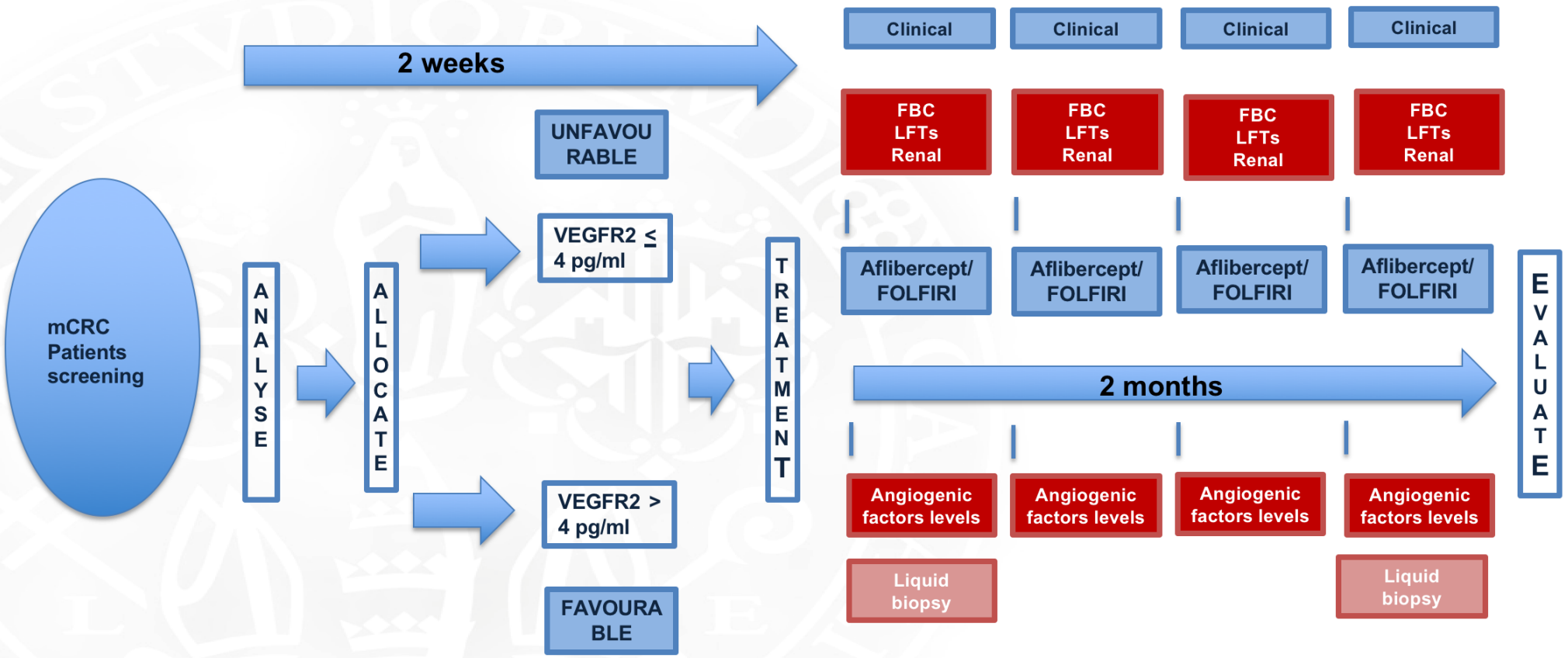
Abbreviations: CEC, circulating endothelial cells; CECP, circulating endothelial cell precursors; DCE-CT, dynamic contrast-enhanced computed tomography;

Potential biomarkers identified from the VELOUR study

Biomarker	Median	High or Low biomarker group	Hazard Ratio (ZT vs control)	p-value*	Interaction p-value
IL-8	20 pg/ml	High	0.63	0.0004	0.022
MIF	0.3 ng/ml	High	0.67	0.003	0.087
VEGF	142 pg/ml	High	0.64	0.0013	0.056
VEGFR2	4.2 pg/ml	High	0.69	0.0082	0.157^
VEGFR3	35 ng/ml	High	0.69	0.0061	0.177^
SPD	7.7 ng/ml	Low	0.60	0.0003	0.003

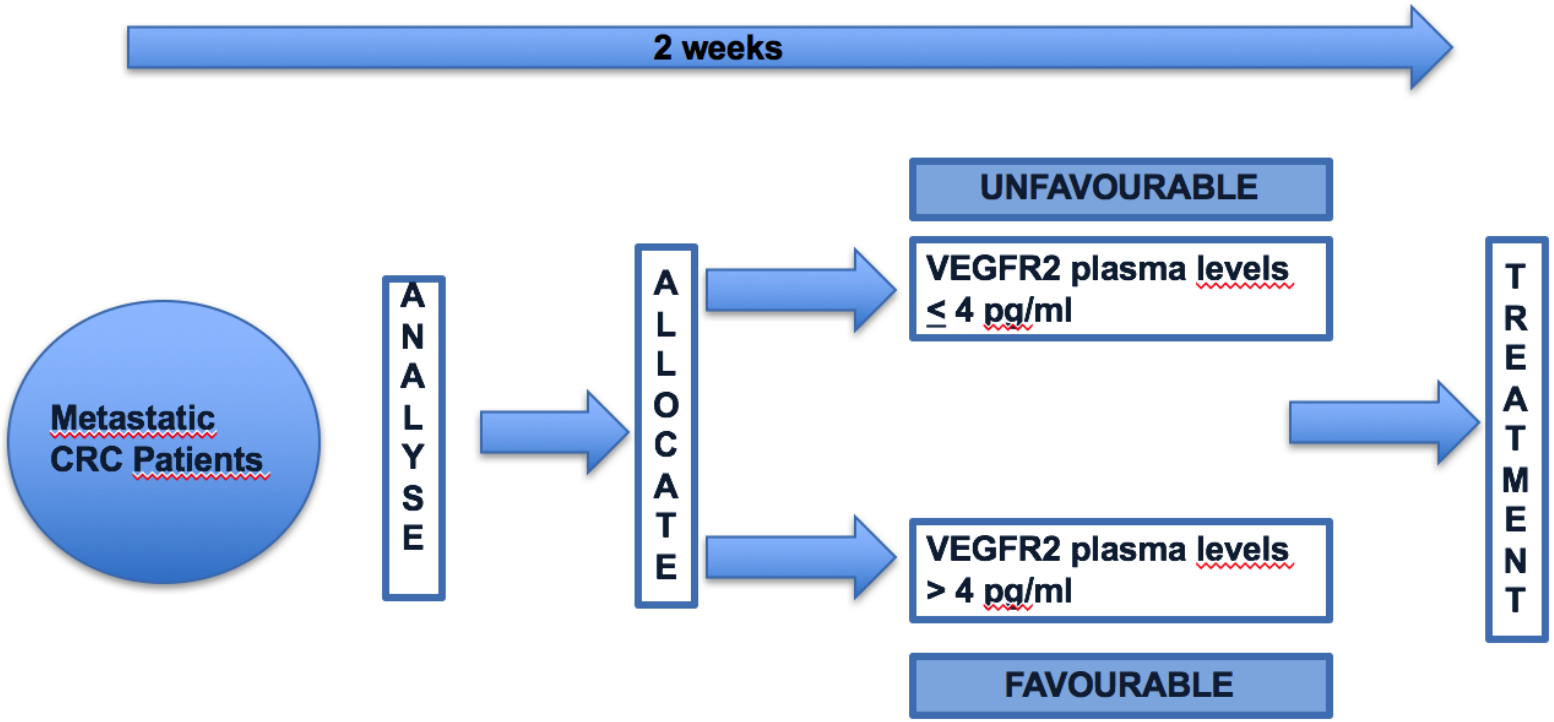
Sims TN, et al. ASCO-GI 2015 #799

Study design



- RAS WT
- Progression after first line oxaliplatin/fluoropyrimides in combination with an anti-EGFR antibody
- ECOG < 2
- Written informed consent

Study design



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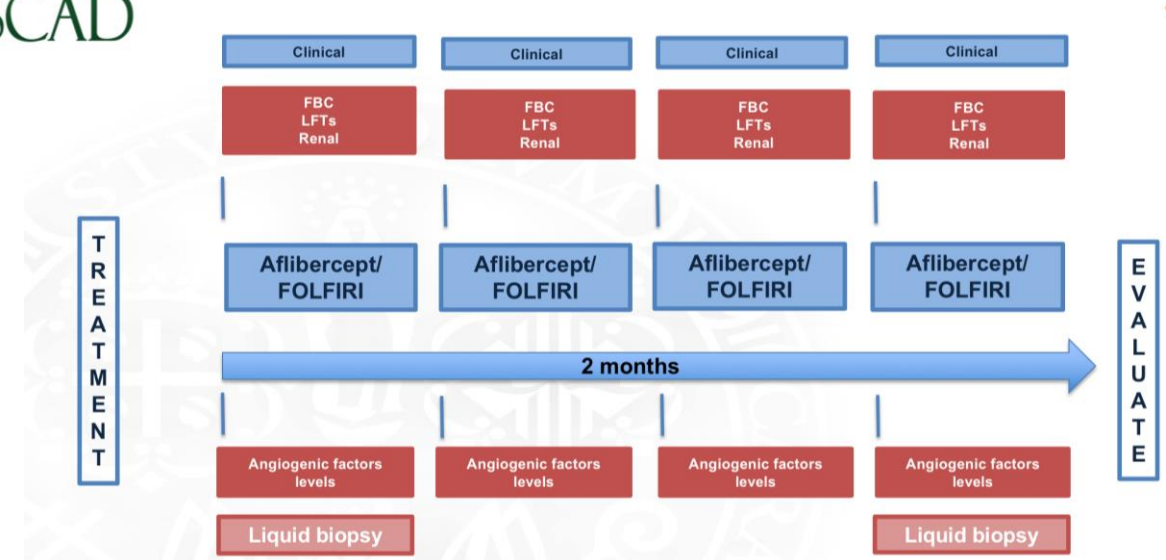

Treatment duration:
until PD, unacceptable toxicity or consent withdrawal

Liquid biopsy
every 8 weeks

Circulating biomarker:
before each cycle

VEGFR2	VEGF	PlGF	HGF	VEGFR1	IL8	IL1
Tcad	VEGFR3	SAP	VDBP	NRP1	CRP	Endoglin

ABL1	EGFR	GNAS	KRAS	PTPN11
AKT1	ERBB2	GNAQ	MET	RB1
ALK	ERBB4	HNF1A	MLH1	RET
APC	EZH2	HRAS	MPL	SMAD4
ATM	FBXW7	IDH1	NOTCH1	SMARCB1
BRAF	FGFR1	JAK2	NPM1	SMO
CDH1	FGFR2	JAK3	NRAS	SRC
CDKN2A	FGFR3	IDH2	PDGFRA	STK11
CSF1R	FLT3	KDR	PIK3CA	TP53
CTNNB1	GNA11	KIT	PTEN	VHL

Endpoints

FONDAZIONE GISCAD

PRIMARY ENDPOINT:

OS according to VEGFR2 levels

SECONDARY ENDPOINTS:

- OS
- PFS
- RR
- Toxicity Profile defined according to CTCAE v. 4.03
- Angiogenetic factors levels concentration

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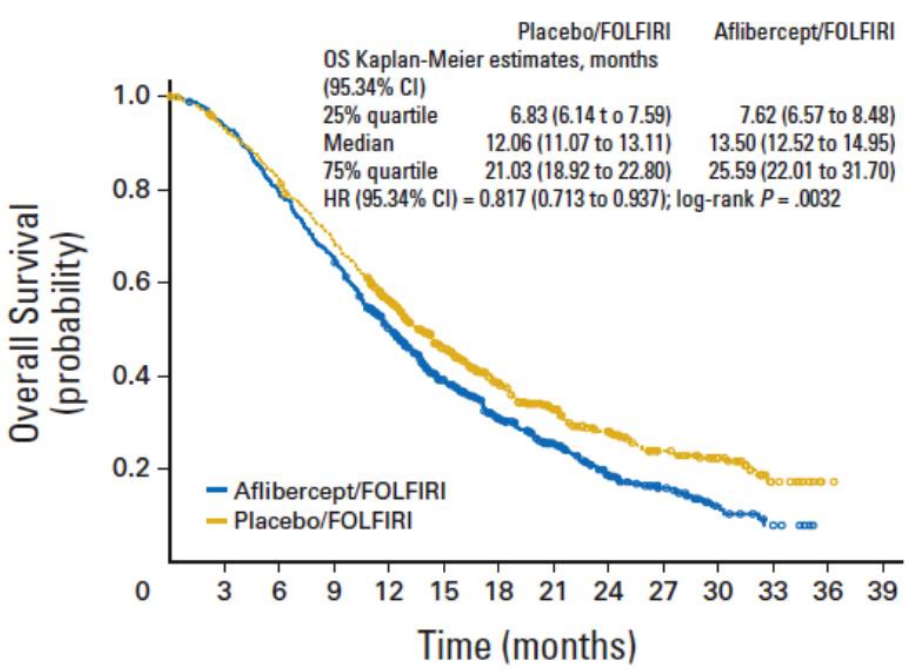
Statistical considerations



Sample size: 151 pts

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Inclusion and exclusion criteria

Inclusion Criteria:

- Histological confirmation of colorectal cancer
- Confirmed RAS wild type patient treated with an oxaliplatin-anti EGFR treatment in 1st line
- At least one lesion measurable with CT or MRI scan
- Radiologically documented progressing disease after FOLFOX in combination with an anti-EGFR monoclonal antibody (either cetuximab or panitumumab)
- Life expectancy ≥ 3 months
- Netrophils count 3 1.5 x 109/L
- Platelets count 3 100 x 109/L
- Hemoglobin 3 9 g/dL
- Creatinine £ 1.5 mg/dL, Proteinuria <2+ (dipstick urinalysis) or ≤1g/24hour.Bilirubin £ 1.5 x ULN
- AST and ALT £ 2.5 x ULN (< 5 ULN in case of liver metastases)
- Informed written consent
- ECOG Performance Status £ 2
- Age ≥18 yrs
- Regular follow-up feasible.
- For female patients of childbearing potential, negative serum pregnancy test within 1 week (7 days) prior of starting study treatment,
- Female patients must commit to using reliable and appropriate methods of contraception until at least three months after the end of study treatment (when applicable). Male patients with a partner of childbearing potential must agree to use contraception in addition to having their partner use another contraceptive method during the trial.

Exclusion Criteria:

- Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy),
- Treatment with any other investigational medicinal product within 28 days prior to study entry.
- Other serious and uncontrolled non-malignant disease,
- History or evidence upon physical examination of CNS metastasis unless adequately treated
- Gilbert's syndrome
- Intolerance to atropine sulfate or loperamide
- Known dihydropyrimidine dehydrogenase deficiency
- Treatment with CYP3A4 inducers unless discontinued > 7 days prior to randomization
- Any of the following in 3 months prior to inclusion: grade 3-4 gastrointestinal bleeding (unless due to resected tumor), treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, or diverticulitis.
- Other concomitant or previous malignancy, except: i/ adequately treated in-situ carcinoma of the uterine cervix, ii/ basal or squamous cell carcinoma of the skin, iii/ cancer in complete remission for >5 years,
- Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 days
- Pregnant or breastfeeding women,
- Patients with known allergy to any excipient to study drugs,
- History of myocardial infarction and/or stroke within 6 months prior to randomization, NYHA class III and IV congestive heart failure
- Bowel obstruction.
- Uncontrolled infections
- Known drugs or alcohol abuse
- Severe cardiovascular disease

DISTINCTIVE TRACKING SHOT: 10 october

CENTRO	P.I.	ATTIVAZIONE	N° TOTALE
Padova	Loupakis	04/20/2018	19
Cagliari	Scartozzi	04/09/2018	9
MI - ICH	Rimassa	04/10/2018	4
Bergamo - Gavazz.	Beretta	09/27/2018	2
Bergamo hpg 23	Mosconi	10/15/2018	2
MI - IEO	Zampino	09/18/2018	1
Brescia	Zaniboni	01/18/2019	3
Meldola	Frassineti	10/25/2018	-
MI - S. Carlo	Moroni	11/23/2018	-
Modena	Luppi	03/06/2019	1
Napoli - INT	Avallone	06/22/2018	-
Negrar (VR)	Gori	08/28/2018	-
Nuoro	Sarobba	07/31/2018	-
Palermo - La Maddalena	Gebbia	11/05/2018	-
Piacenza	Cavanna	01/17/2019	-
Potenza	Bilancia	11/02/2018	3
Rho (MI)	Della Torre	11/19/2018	-
Udine	Pella	09/04/2018	-
Aviano	Buonadonna		
Cagliari - Businco	Mascia		
Lanciano (CH)	Biondi		
Lecce	Leo		
Napoli ASL1 - Centro	Daniele		
Roma FBF	Corsi		
Tor Vergata (RM)	Formica		
Treviglio	Petrelli		
Tricase (LE)	Tamburini		
Vicenza	Aprile		
		TOTALE PAZIENTI	44

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