

CLINICAL IMPLICATIONS OF THE PRESENCE OF CTCs POSITIVE FOR VEGFR EXPRESSION IN PATIENTS WITH ADVANCED COLORECTAL CÁNCER UNDERGOING TREATMENT FOR FOLFOX+BEVACIZUMAB.

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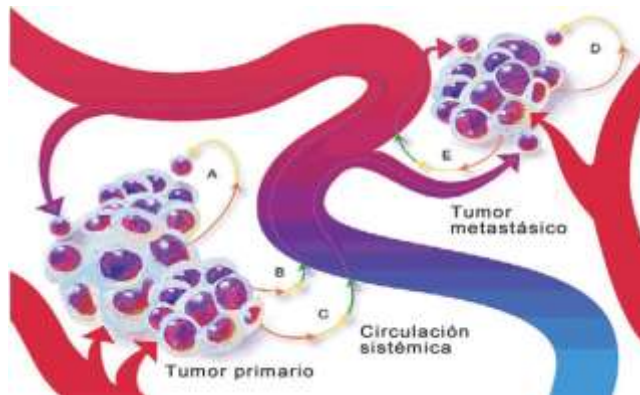
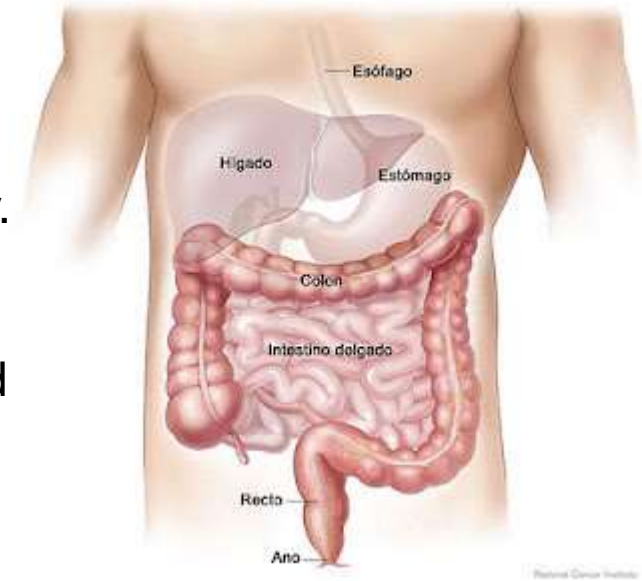
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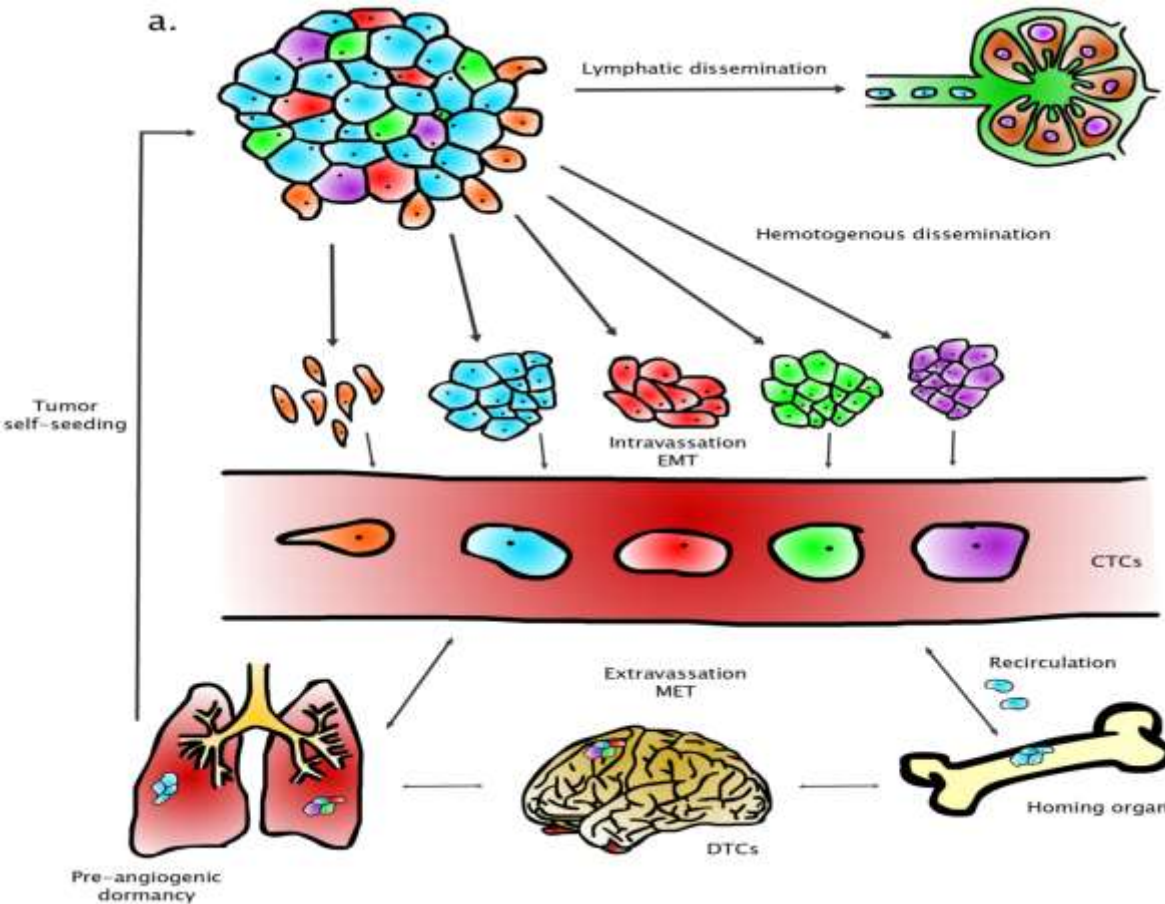
OVERVIEW

Colorectal cancer (CRC) is one of the most common forms of cancer, in regard to both incidence and mortality. In the Western world, CRC is the second most common malignancy diagnosed in women, after breast cancer, and the third most common in men, after prostate and lung cancer, accounting for 13.1% and 12.8% of all forms of cancer, respectively

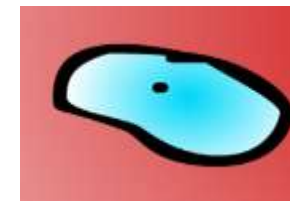


For the time being, surgical resection of the tumor remains the prominent choice for treatment followed by adjuvant chemotherapy.

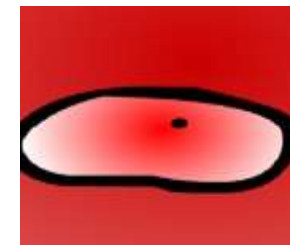
Metastasis process



CETUXIMAB
PANITUMUMAB



?



AFLIBERCEP
BEVACIZUMAB

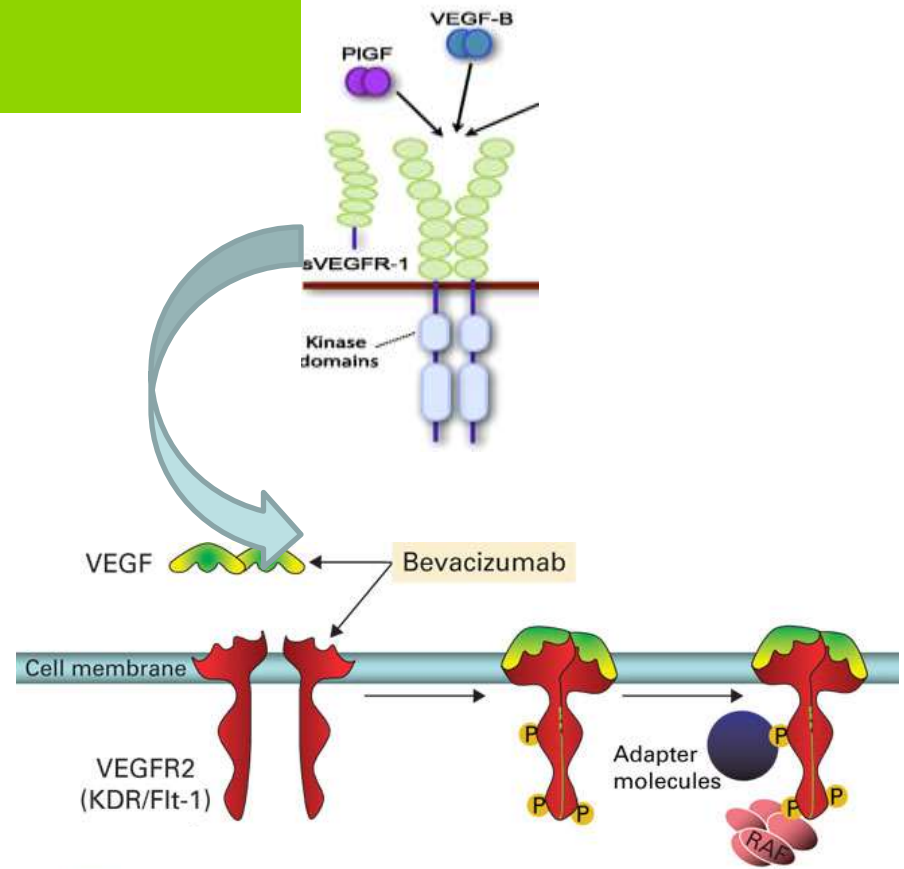
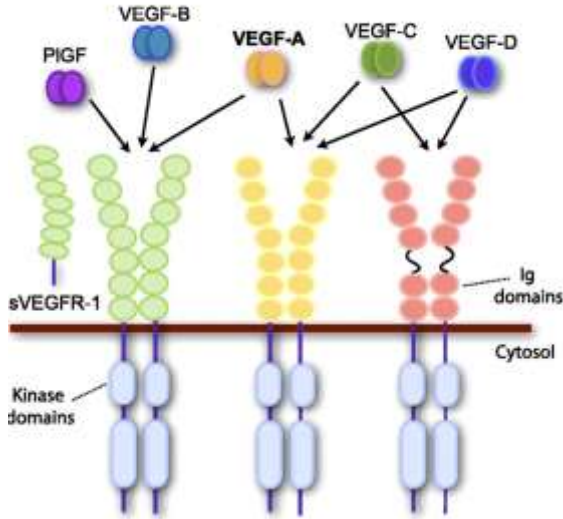


REGORAFENIB

Serrano MJ et al. Expert Review. 2013

RATIONAL VEGF-VEGFR

- Proliferation
- Metastases



Pattern of expression of VEGFR in CTCs

Material and Methods

- A Prospective study.
- 50 patients enrolled with metastatic colon cancer
- 10 ml of whole blood were drawn from colon cancer patients into the CellSave Preservative Tube containing a cellular preservative and processed within 72 hours
- MACs Miltenyi system was then utilized to separate the CTCs by treatment with iron particles coated with antibodies against cytokeratine for capturing CTCs
- Multi-Cytokeratin antibody (AE1/AE3) was used to detect CTCs by immunohistochemistry method.

LANDMARK STUDY

		N(%) Basal		N(%) week 6		N(%) week 12		N(%) week 24	
		CTC-	CTC+	CTC-	CTC+	CTC-	CTC+	CTC-	CTC+
Age	<50	6 (46.2)	7 (53.8)	4 (40)	6 (60)	5 (55.6)	4 (44.4)	6 (75)	2 (25)
	>50	20 (54.1)	17 (45.9)	14 (50)	14 (50)	12 (52.2)	11(47.8)	14 (70)	6 (30)
Sex	Man	17 (53.1)	15 (46.9)	12 (48)	13 (52)	10 (45.5)	12(54.5)	14 (73.7)	5 (26.3)
	Woman	8 (44.4)	10 (55.6)	7 (53.8)	6 (46.2)	7 (70)	3 (30)	6 (66.7)	3 (33.3)
Menopausal state	Pre	1 (25)	3 (75)	1 (33.3)	2 (66.7)	1 (50)	1(50)	1 (100)	0 (0)
	Post	7 (50)	7 (50)	6 (60)	4(40)	6 (75)	2 (25)	5 (62.5)	3 (37.5)
Tumor location	Rectum	22 (54.5)	10 (45.5)	9 (52.9)	8 (47.1)	9 (64.3)	5 (35.7)	7 (70)	3(30)
	Left colon	5 (31.25)	11 (68.75)	5 (38.5)	8 (61.5)	7 (63.6)	4 (36.4)	9 (81.8)	2 (18.2)
	Transverse colon	3 (75)	1 (25)	3 (75)	1 (25)	0 (0)	3 (100)	2 (66.7)	1 (33.3)
	Right colon	6 (75)	2 (25)	2 (50)	2 (50)	1 (25)	3(75)	3 (75)	1 (25)
KRAS	Wild type	10 (50)	10 (50)	9 (52.9)	8 (47.1)	11 (73.3)	4 (26.7)	10 (66.7)	5 (33.3)
	Mutated	8 (47.1)	9 (52.9)	6(40)	9 (60)	5 (38.5)	8 (61.5)	9 (75)	3 (25)
	unknown	8 (61.5)	5 (38.5)	4 (66.7)	2 (33.3)	1 (25)	3 (75)	1 (100)	0 (0)
Metástasis location	1 organ	18 (60)	12 (40)	13 (54.2)	11 (45.8)	10 (47.6)	11 (52.4)	13 (68.4)	6 (31.6)
	> 1 organ	8 (40)	12 (60)	6 (42.9)	8 (57.1)	7 (63.6)	4 (36.4)	7 (77.8)	2 (22.2)

1. CTC detection and their correlation with clinical-pathological characteristics

2. Expression of VEGF Receptor in CTCs and their relation with response to Bevacizumab.

STUDY METHOD

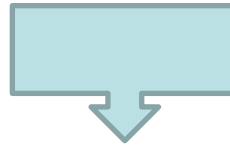
BLOOD DRAWN AT BASELINE



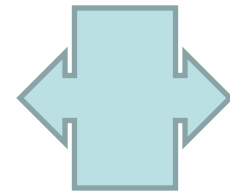
BLOOD DRAWN 6 WEEKS



BLOOD DRAWN 12 WEEKS



ASSESSMENT OF TREATMENT RESPONSE
USING RECIST CRITERIA



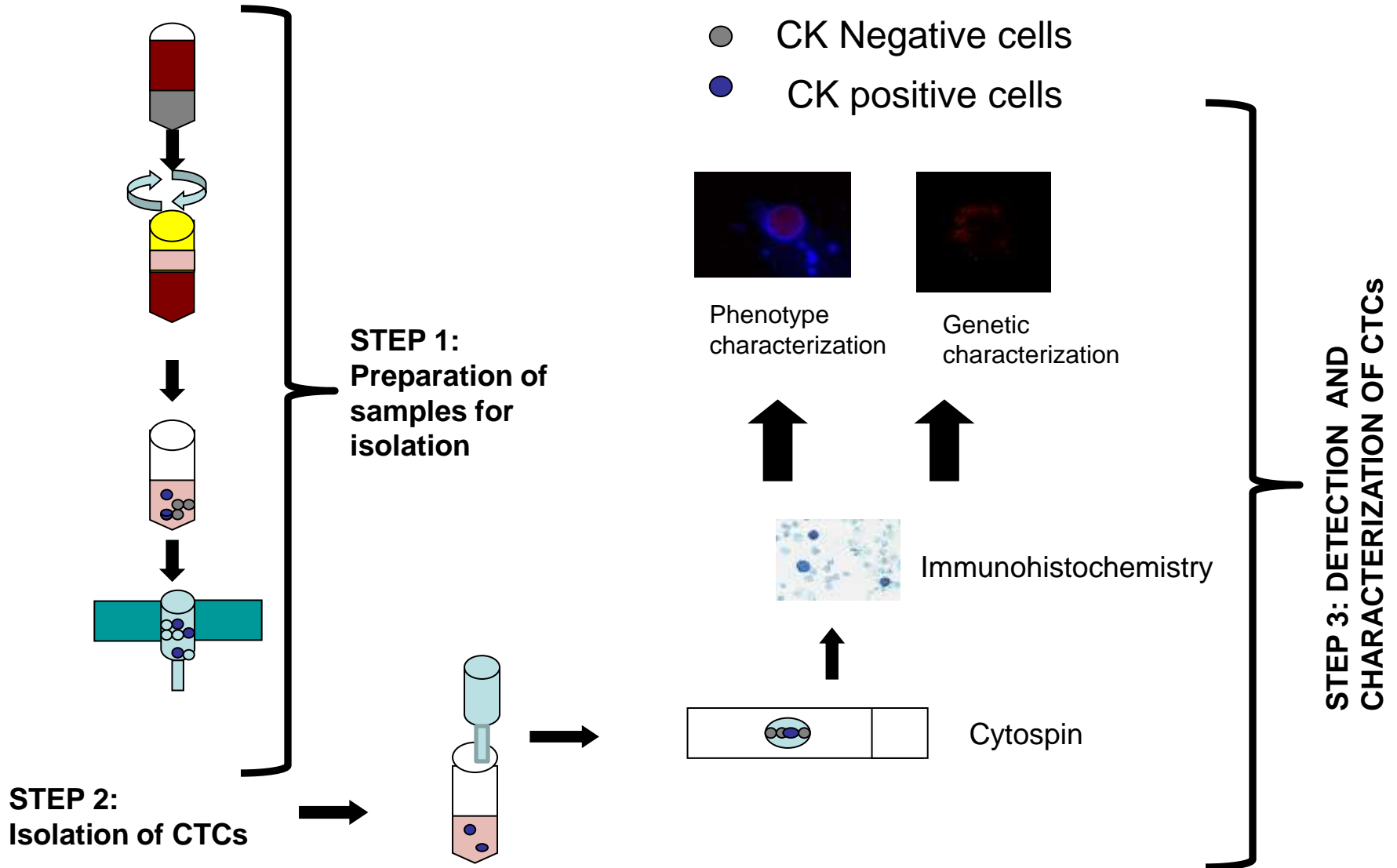
IF POSITIVE RESPONSE

BLOOD DRAWN 24 WEEKS AFTER
AFTER INITIAL TREATMENT
:FOLFOX+BEVAZUCIMAB

IF NEGATIVE RESPONSE

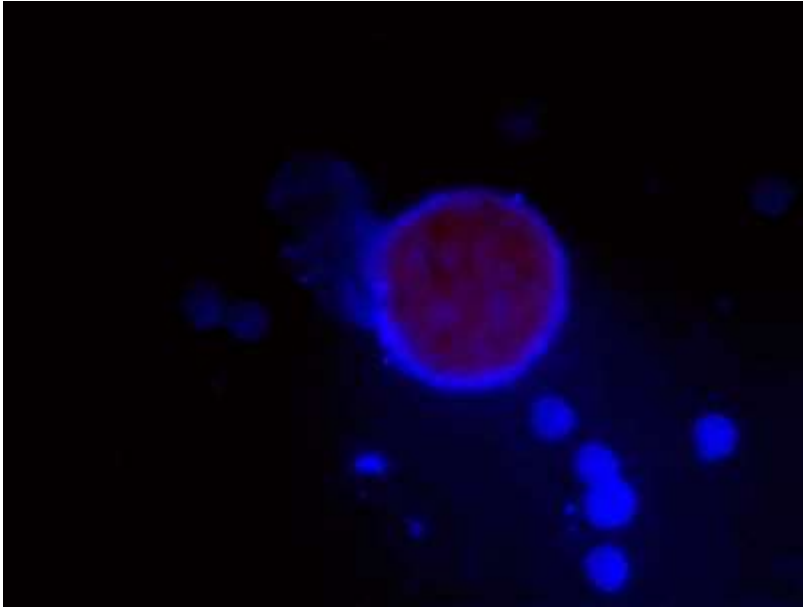
Patient is excluded from this study

ISOLATION AND DETECTION METHOD

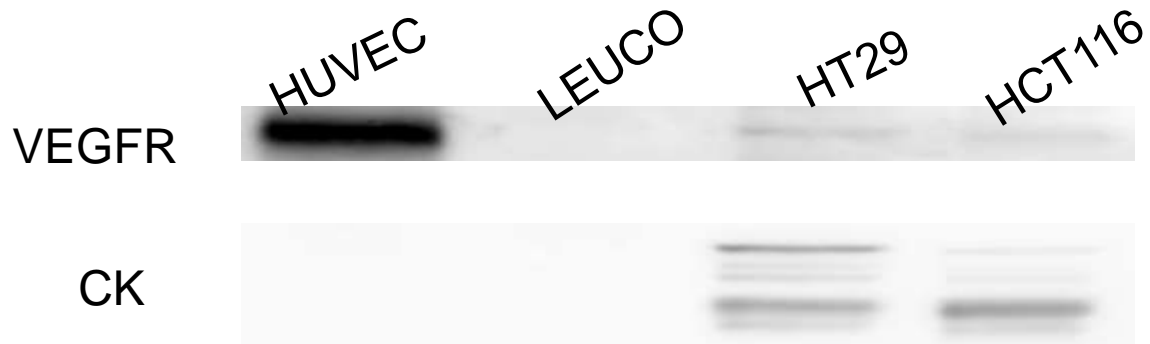
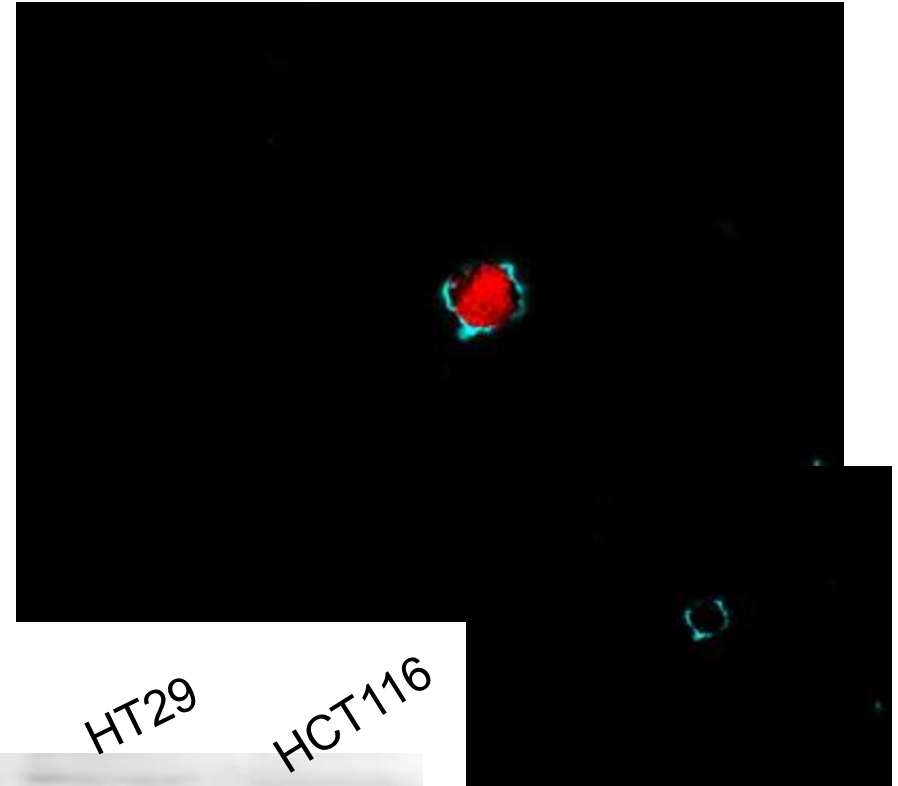


RESULTS

HUVE cell line. Positive Control for expression of VEGFR.



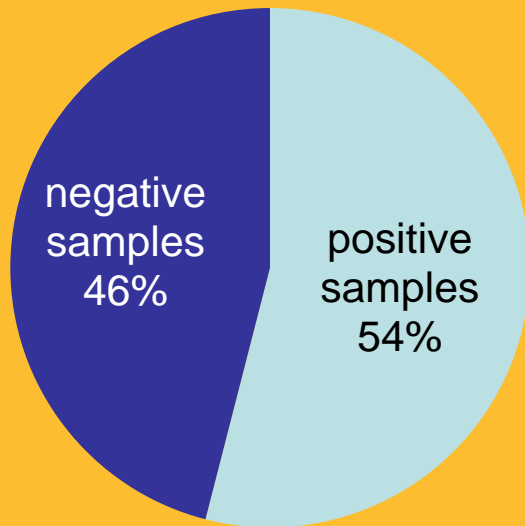
CTCs positive sample for VEGFR and CK expression from a MCC patients



RESULTS

- Immunocytochemistry for CK expression was performed on 50 samples and 27 (54%) of cases were positive for CK.

% of patients positive for CTCs at baseline



AVERAGE NUMBER OF CTCs DETECTED DURING FOLLOW-UP

	Baseline	6 weeks	12 weeks	24 weeks
CTC ratio	1-100	1-40	1-40	1-15

RESULTS

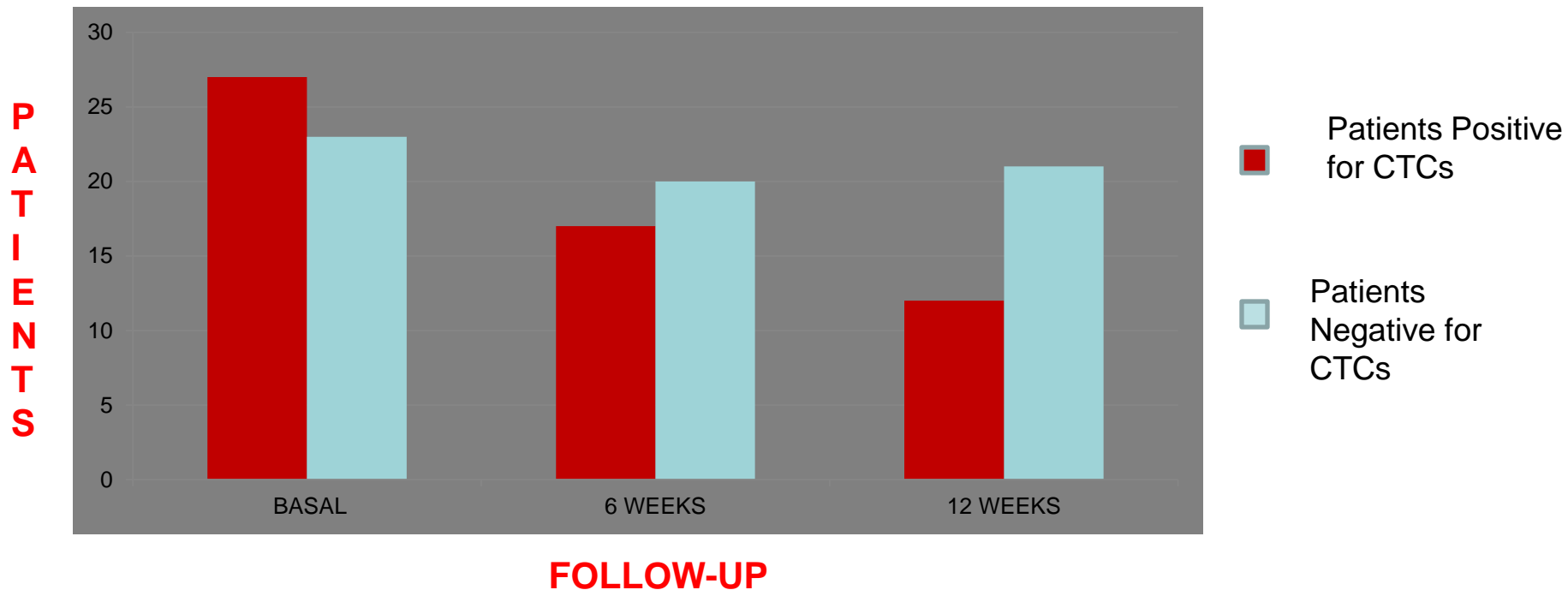
	Baseline <i>P</i>	6 Weeks <i>P</i>	12 weeks <i>P</i>
Age	NS	NS	NS
Sex	NS	NS	NS
Tumor location	NS	NS	NS
K-ras	NS	NS	NS
Metastas is location	NS	NS	NS

No positive correlation was found between CTCs and clinical- pathological characteristics

RESULTS

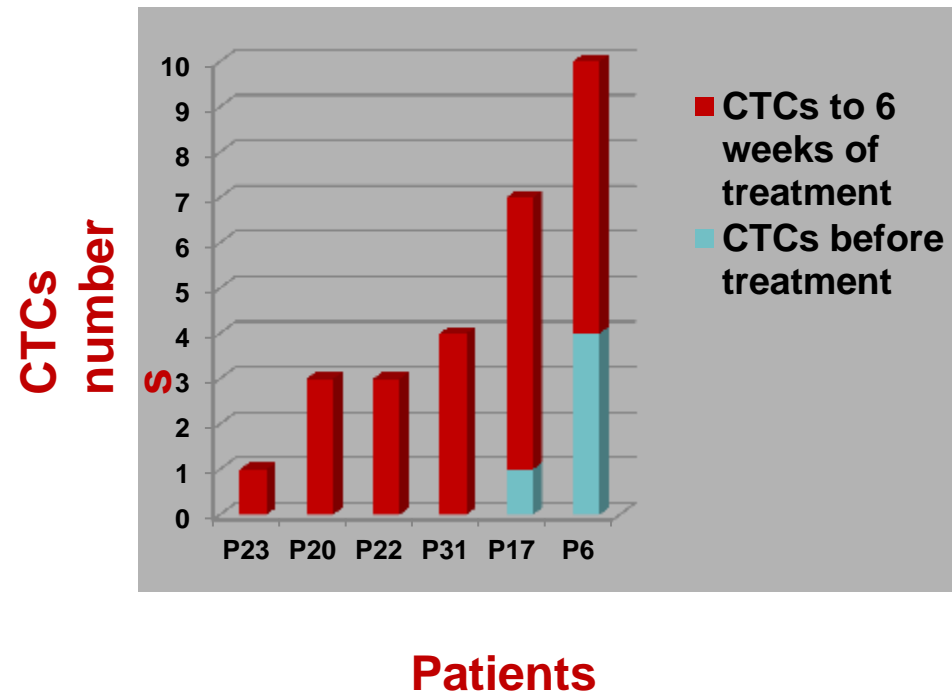
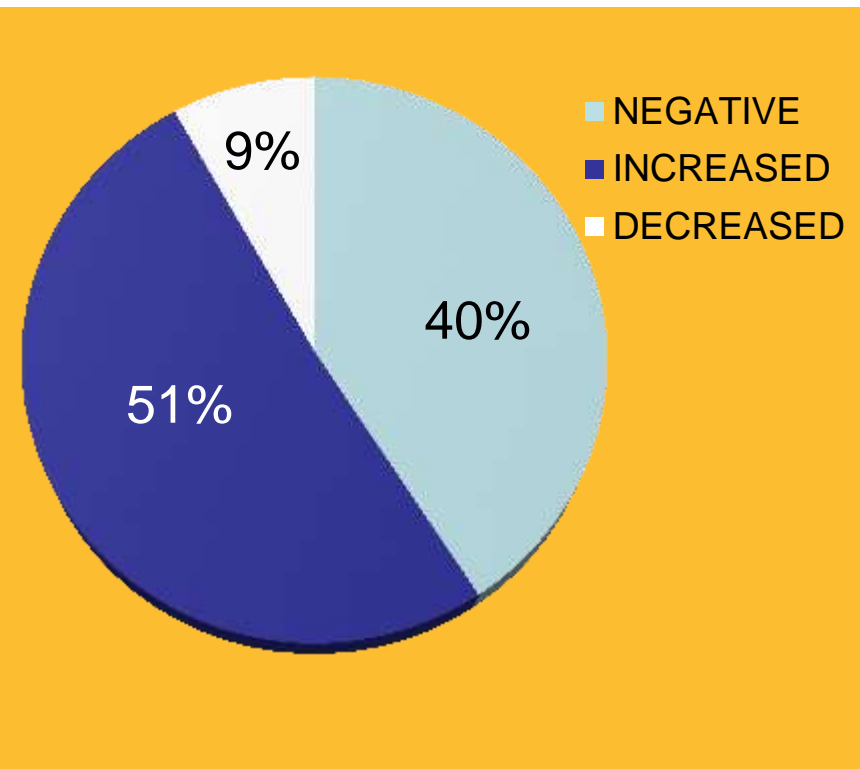
PREVALENCE OF CTCs :

EVALUATION OF THE PRESENCE OR ABSENCE OF CTCs AT 6 AND 12 WEEKS DURING FOLLOW-UP



RESULTS

- After treatment the prevalence of CTCs was shown in the 60% of patients :

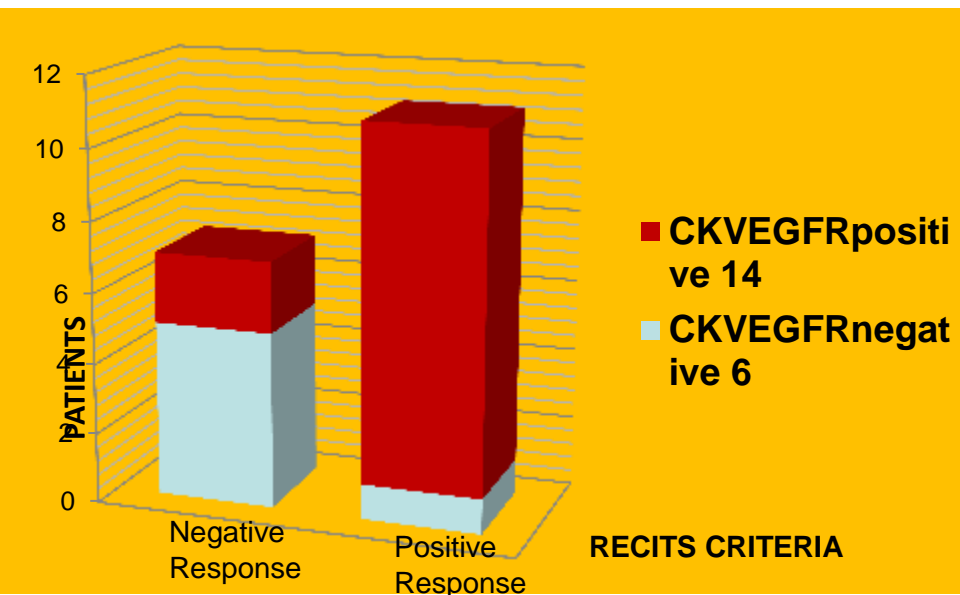
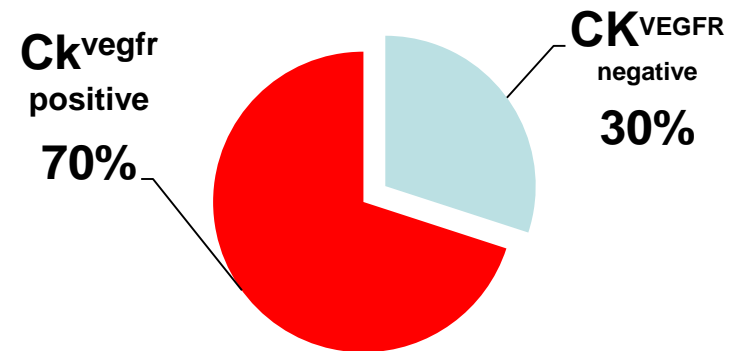


RESULTS

■ Characterization of CTCs based on the VEGFR expression:

- 30 % of CTC were negative for VEGFR
- 70% of CTC were positive for VEGFR

CTC-VEGFR POSITIVES AT BASALINE



88% of patients with CTC^{VEGFR+}
IMPROVED PFS with positive response

83.3% of patients with CTC^{VEGFR-}
Developed a negative response and short PFS

CONCLUSIONS

Our findings indicate that VEGFR-2 can be expressed in CTCs.

We found that VEGFR-2 was expressed in most metastatic colon cancer CTCs.

Our study indicates the presence of heterogeneity in VEGFR distribution among the population of CTCs analyzed in the same sample, identifying two subpopulations: $CTC^{CK/VEGFR+}$ and $CTC^{CK/VEGFR-}$

In this study, we observed a negative response to FOLFOX+Bevacizumab treatment in patients $CTC^{CK/VEGFR-}$ while the patients with $CTC^{CK/VEGFR+}$ responded favorably to Treatment with FOLFOX+Bevacizumab.

Biomarker Characterization of Circulating Tumour Cells in Colon Cancer Patients

- **B**iomarker characterization in CTCs may become a useful tool for selecting patients for tailored therapies and targeted drug development.
- **T**he mere detection of CTCs is not sufficient to understand the biological properties of the cells. Specific biologic characterization of all types of CTCs will be necessary for eventual clinical application.
- **O**ur study also suggests that more importance must be placed on CTC phenotypes when determining an appropriate treatment regimen instead of basing all treatment solely on primary tumor type.

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¡MUCHAS GRACIAS!

THANK YOU SO MUCH!



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