Circulating epidermal growth factor-like domain 7 has prognostic impact in patients with metastatic colorectal cancer

Torben F. Hansen[1,4], MD, PhD, Dorte A. Olsen[2,4], MSc, Flemming Brandt Sørensen[3,4], MD, DMSc, and Anders Jakobsen[1,4], MD, DMSc

Departments of [1]Oncology, [2]Biochemistry, and [3]Clinical Pathology, Vejle Hospital, Part of Lillebaelt Hospital, Vejle, Denmark, [4]Institute of Regional Health Research, University of Southern Denmark, Denmark
email: torben.hansen@rsyd.dk

Background

- Four anti-angiogenic drugs are currently approved for the treatment of patients with metastatic colorectal cancer (mCRC).
- This number is expected to grow.
- The clinical benefit, when used in unselected patient cohorts, is often modest.
- This calls for a better understanding of the targeted biology in order to select patients and treatment in a more appropriate way.
- Epidermal growth factor-like domain 7 (EGFL7) is a key regulator of the angiogenic process responsible for vascular tube formation, vascular integrity, and for the guiding of migrating endothelial cells during the vascular sprouting process.

Aim

- To analyse the relationship between circulating EGFL7 (cir-EGFL7) and clinical outcome in patients with mCRC treated with first line capecitabine and oxaliplatin (CAPOX), and bevacizumab.

Table 1. Patient Characteristics

	Patients N = 89
Gender	
Male	53 (60)
Female	36 (40)
Age (years)[a]	
Mean (SD)	65 (10)
Range	32-80
> Mean	55 (62)
≤ Mean	34 (38)
ECOG PS	
0	58 (65)
1-2	31 (35)
Tumour resection	
Yes	28 (31)
No	61 (69)
Localization	
Colon	53 (60)
Rectum	34 (38)
Synchronous	2 (2)
Met. sites	
1	40 (45)
≥2	49 (55)
Adjuvant chemotherapy	
Yes	6 (7)
No	83 (93)
KRAS	
Wild type	21 (24)
Mutated	23 (26)
Unknown	45 (51)

N: Number; SD: Standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; Met. sites: Number of metastatic organ sites
Not all sums of percentages equals 100% due to rounding of data
[a]Age at start of treatment

Material and methods

Study population, sampling and treatment
- The study included 89 patients with mCRC allocated in the period from March 2010 to October 2013.
- Serum samples were collected at base-line and every three weeks until progression.
- All patients received first line CAPOX (consisted of a 2-hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 followed by oral capecitabine 1000 mg/m^2 twice daily on days 1 through 14 of a 21-days cycle) and bevacizumab (7.5 mg/kg on day 1).

Evaluation and tumour response criteria
- The response to treatment, according to RECIST version 1.0, was assessed by CT scans of the chest and abdomen.

Protein analyses
- An enzyme-linked immunosorbent assay, (Cloud-Clone Corp.) was used to quantify EGFL7 in serum samples according to the manufacturer's protocol.
- All samples were assayed in duplicate and the average was used for comparison with clinical data. Precision was acceptable, in that total coefficients of variation on two levels were 19.2% (high) and 23.4% (low). Protein concentrations are expressed in ng/ml.

Statistical analyses
- The association between categorical outcomes and the EGFL7 concentrations was analysed using the Wilcoxon Rank-Sum Test for differences in medians. Progression free survival (PFS), and overall survival (OS), was compared using the Kaplan-Meier method and the log rank test, and patients were classified according to EGFL7 concentrations at base-line (low, intermediate and high).

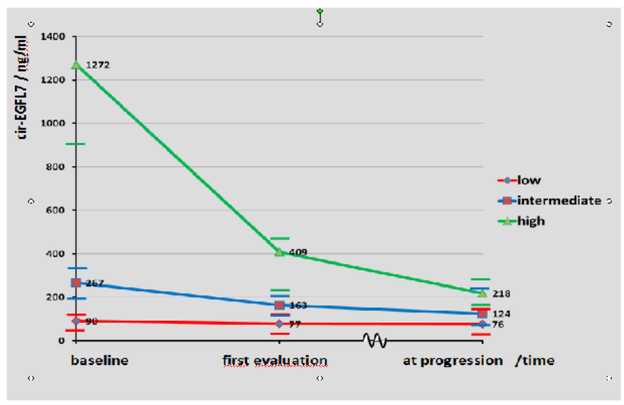

Figure 1. Median cir-EGFL7 levels at base-line, first evaluation, and at progression grouped according to EGFL7 concentrations at base-line. The upper limit (2003 ng/ml) of the 95% confidence interval for the high cir-EGFL7 levels at baseline is censored for graphical reasons but not from the analyses.

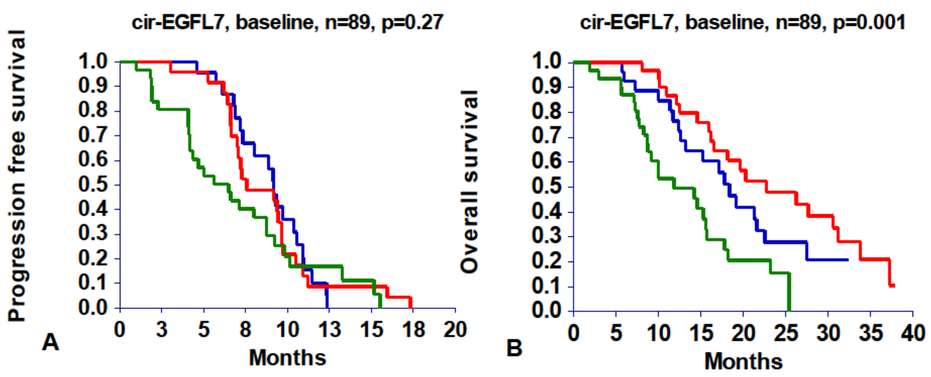

Figure 2. Progression free survival (A) and overall survival (B) curves according to cir-EGFL7 concentrations at base-line. The red curves illustrate patients with low concentrations, blue curves patients with intermediate concentrations, and green curves patients with the highest concentrations.

Results

Patient characteristics
- Patient characteristics are shown in Table 1.

Circulating EGFL7
- A significant decline in cir-EGFL7 was detected after treatment initiation (Figure 1), p<0.001.

Prognoses
- Circulating EGFL7 was not related to PFS, but was correlated with OS. Median OS for patients with high base-line concentrations was 11.8 months (95% confidence interval (CI), 8.8-15.6 months), 18.4 months (95% CI, 13.2-21.6 months) in the intermediate group, and 22.7 months (95% CI, 16.5-30.6 months) in the low group, respectively, p=0.001 (Figure 2 A and B).
- The unfavourable prognosis for patients with high levels of circulating EGFL7 at base-line was independent of performance status, prior tumour resection, and number of metastatic sites when analysed in a Cox Regression multiple analyses, hazard ratio 2.53 (95% CI 1.23-5.21), p=0.01 (Table 2).
- Base-line concentrations (medians) of EGFL7 were significantly lower in patients that post-treatment underwent resections of their metastases (R0 resections), 143 ng/ml (95% CI, 68-225 ng/ml), N=16, compared to the remaining patients, N=73, that remained unresectable, 336 ng/ml (95% CI, 195-514 ng/ml), p=0.01 (Fig. 3).
- Circulating EGFL7 was not related to tumour response.

Table 2. Cox Regression analyses, simple and multiple

	simple analysis			multiple analysis		
	HR	95 % CI	p-value	HR	95 % CI	p-value
Gender						
Female	0		0.8910			
Male	0.9647	0.5771-1.6127				
Age (years)[a]	1.0095	0.9833-1.0364	0.4797			
ECOG PS						
0	1		**0.0161**	1		0.2920
1-2	1.9118	1.1280-3.2402		1.3644	0.7655- 2.4321	
Tumour resection						
No	1		0.0542	1		0.4016
Yes	0.5749	0.3272-1.0100		0.7560	0.3932- 1.4534	
Localization[b]						
Rectum	1		0.1319			
Colon	1.5179	0.8820-2.6121				
Metastatic sites						
1	1		**0.0179**	1		**0.0322**
≥2	1.9117	1.1183-3.2680		1.9013	1.0561- 3.4229	
Adjuvant chemotherapy						
No	1		0.4588			
Yes	0.6434	0.2003-2.0664				
cir-EGFL7						
Low	1			1		
Intermediate	1.5445	0.7968-2.9937	0.1980	1.4770	0.7586- 2.8757	0.2513
High	3.1143	1.6345-5.9338	**0.0006**	2.5339	1.2313- 5.2144	**0.0116**

HR: hazard ratio; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; cir-EGFL7: circulating epidermal growth factor-like domain 7
[a]Age is included in the analyses as a continuous numerical, numerical value
[b]The two patients with synchronous tumours were not included in the analyses

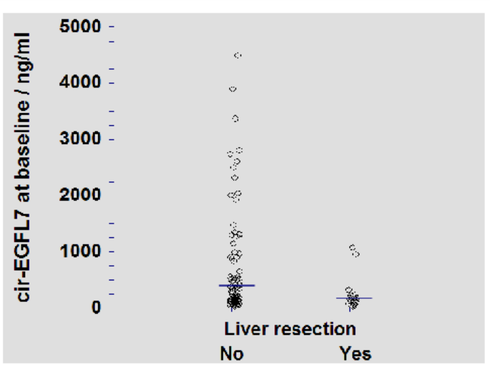

Figure 3. Base-line concentrations (medians) of EGFL7 were significantly lower in patients that post treatment underwent resections of their metastases (R0 resections), 143 ng/ml (95% CI, 68-225 ng/ml), N=16, compared to the remaining patients, N=73, that remained unresectable, 336 ng/ml (95% CI, 195-514 ng/ml), p=0.01.

CONCLUSION

The present results confirm unfavourable clinical outcome for patients with high concentrations of EGFL7, *thus*, supporting the potential of targeting EGFL7 in the setting of mCRC.

WCGC 2015
238--P
Clinical Colon Cancer
Torben Hansen
DOI: 10.3252/pso.eu.17wcgc.2015
Poster presented at: 17th World Congress on Gastrointestinal Cancer, 1-4 JULY 2015, BARCELONA, SPAIN