web meeting

News da **ASCO GI 2014**

Stefano Cascinu

Come cambia l'approccio terapeutico al Carcinoma Gastrico in fase

- adiuvante
- avanzata
- metastatica

Carcinoma del colon retto in fase

- adiuvante
- avanzata
- metastatica

2014
Gastrointestinal
Cancers Symposium

ASCO GI 2014

Carcinoma dell'esofago, stomaco e colon-retto: che cosa c'è di nuovo.

- Prevenzione
- Terapia adiuvante/neoadiuvante
- Terapia della fase avanzata

2014
Gastrointestinal
Cancers Symposium

Esofago

- **Trattamento per stadi precoci**
  - **Displasia di alto grado (39% dei casi ca invasivo); Barret: resezione endoscopica e se no ca invasivo ablazione con radiofrequenza**
  - **Ca intramucoso: resezione endoscopica (recidiva invasiva 11%; 5y OS 98%**
  - **Ca sottomucoso: resezione endoscopica: attenzione (22% linfonodi positivi)**

2014 Gastrointestinal Cancers Symposium

Esofago

- **Terapia della fase avanzata: inibizione di EGFR non fornisce vantaggi: lo studio RT 0436**

344 pazienti randomizzati a paclitaxel/ cisplatino/RT +/- cetuximab: uguale risposta, uguale sopravvivenza a 2 anni (44% vs 41.7%)

2014
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Cancers Symposium

Carcinoma gastrico

- **HP e carcinoma gastrico: infiammazione ed instabilità genetica: prevenzione primaria**

- **Tecniche di endoscopia molecolare: diagnosi precoce**

2014 Gastrointestinal Cancers Symposium

Carcinoma gastrico: non una ma molte neoplasie

30 General Poster Session A (Board #A40), Thu, 12:00 PM-2:00 PM and 5:30 PM-7:00 PM

Gastric cancer (GC) in California Cancer Registry (CCR): One disease, many faces. *Presenting Author: Afsaneh Barzi, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: In the US there are approximately 21,000 newly diagnosed GCs with California having the highest number of reported cases per year. Given the disparity in the incidence of the disease among Asians and Hispanics we conducted an analysis of GCs in the CCR to assess the differences in the presentation and outcome of the reported cases from 2000 to 2010. **Methods:** We identified 26,645 GCs inclusive of Asian, Hispanic, and non-Hispanic whites (NHW); 20% of our population is Asian and 30% of is Hispanic. We examined the tumor characteristics (demographics, stage, anatomical subsite), age adjusted incidence rates (AAIR), and survival among Asian and Hispanic patients as compared to NHW. **Results:** AAIR per 100,000 individuals is 5.87 (95% CI: 5.77-5.97) for NHW, 11.74 (95% CI: 11.46-12.02) for Hispanics and 13.31 (95% CI: 12.96-13.66) for Asians. Among Asians, Koreans have the highest rate and lowest median age of presentation (67ys). In the patients with known stage of the disease (82%) most patients present with stage IV (38%) with no differences in the stage of presentation among different racial/ethnic groups. The male/female (M/F) ratio is different among different racial/ethnic groups. M/F among NHWs is 2.2, followed by 1.8 in Hispanics, and 1.6 in Asians. Among NHW proximal GC (cardia and fundus) is the most common site of presentation (44%), whereas in Asians and Hispanics proximal GC are reported in 14% and 18% respectively. Hazard ratios from Cox regression models adjusted for age, gender, socioeconomic status, nativity, stage, anatomical subsite, and type of treatment received, showed that being of Mexican origin is associated with greater risk of cancer death compared to being NHW (HR = 1.3; 95% CI = 1.2-1.4; $p<0.001$). In contrast Koreans have better survival than NHW (HR = 0.9; 95% CI = 0.8-0.9; $p=0.003$). Prognostic factors for death from gastric cancer included age $>$ 65 and immigration status, with immigrants doing better than US born. **Conclusions:** The observed disparity in the incidence, presentation, and outcome of GC in CCR suggests possible different etiologies that may have implications for the diagnosis and treatment of GC and deserve further exploration.

2014 Gastrointestinal Cancers Symposium

Carcinoma gastrico: attenzione a dove vi fate operare

The effect of postoperative morbidity on survival after resection for gastric adenocarcinoma: Results from the U.S. Gastric Cancer Collaborative. *Presenting Author: Linda X. Jin, Washington University in St. Louis, St. Louis, MO*

Background: The negative impact of postoperative complications (POCs) on survival is well documented for many cancer types, but has not been well described in gastric cancer. Here, we evaluated the effect of POCs on survival after surgery for gastric cancer in a cohort of patients from a multi-institutional database. **Methods:** Patients who underwent surgery with curative intent for gastric adenocarcinoma between 2000-2012 from participating institutions of the U.S. Gastric Cancer Collaborative were analyzed. Patients who died within 30 days of surgery were excluded. Ninety-day postoperative complication data were collected. Survival probabilities were estimated by Kaplan-Meier analysis and compared using the log-rank test. **Results:** A total of 853 patients from seven institutions met inclusion criteria. Median follow-up was 32 months. The overall complication rate was 40% (n=344). The most frequent complications were: infectious (25%, including surgical site infection [8%]), and anastomotic leak (6%). 7% of patients underwent reoperation during the same hospitalization. Five-year overall survival (OS) for patients without perioperative complications was 54%, compared with 39% for patients with POCs (p=0.001). Disease free survival (DFS) at five years was 61% for patients without POCs compared to 49% in patients with POCs (p=0.002). Patients without POCs were significantly more likely to receive adjuvant therapy (55% vs 42%; $p<0.001$). **Conclusions:** In a large, multi-institutional cohort, POCs were associated with decreased survival in patients undergoing surgery for gastric adenocarcinoma. This may be due, in part, to the negative impact of complications on the receipt of adjuvant therapy. Efforts aimed at reducing perioperative morbidity are important not only for short-term surgical outcomes, but also for enhancing long-term oncologic outcomes in patients with gastric cancer.

OS and DFS for patients undergoing surgery with curative intent for gastric cancer stratified by POCs (n=853).

	Patients		
Variable	**+ Complications (n=344)**	**No Complications (n=509)**	***p* value**
5-year OS	39%	54%	0.001
5-year DFS	49%	61%	0.002
Receipt of Adjuvant Therapy	42%	55%	<0.001

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Carcinoma gastrico

- Rainbow trial, uno studio di fase III in seconda linea: paclitaxel +/- ramucirumab
- 665 pazienti
- OS 9.6 vs 7.4 mesi
- PFS 4.4 vs 2.9 mesi
- RR 28% vs 16%
- Effetti collaterali: neutropenia 40.7%; ipertensione 14.1%;

2014 Gastrointestinal Cancers Symposium

Carcinoma gastrico: una terapia personalizzata?

Toward personalized treatment for gastroesophageal adenocarcinoma (GEC): Strategies to address tumor heterogeneity—PANGEA. *Presenting Author: Daniel Virgil Thomas Catenacci, University of Chicago, Chicago, IL*

Background: GEC is the second highest cause of cancer mortality worldwide. The promise of 'personalized' cancer care with therapies toward specific molecular aberrations has potential to improve outcomes. However, there is recognized molecular heterogeneity within GEC (inter-patient heterogeneity), and within an individual (intra-patient heterogeneity) through space (primary tumor to metastatsis) and time (resistance to treatment) - a hurdle to advancing GEC treatment. Current trial design paradigms are challenged by heterogeneity, as they are unable to test targeted therapeutics against low frequency genomic aberrations with adequate power. Accrual difficulties to GEC trials are exacerbated by low frequencies of molecular 'oncogenic drivers.' Oncogenic drivers of GEC including MET and others have even less frequent genomic activation than HER2. To address this challenge, there is need for novel clinical trial designs/strategies implementing novel technologies to account for inter-patient molecular diversity and scarce tissue for analysis. Importantly, there is also need for predefined treatment priority algorithms given multiple aberrations observed within any one individual. Finally, access to multiple therapeutic agents are required to be available for treatment. Intra-patient heterogeneity may be addressed by post-treatment biopsy. **Methods:** We present a novel trial design 'Personalized Anti-Neoplastics for Gastro-Esophageal Adenocarcinoma' for metastatic GEC, integrating medium throughput proteomic/genomic assays with a practical biomarker assessment/treatment algorithm. Analysis of 50 GEC patients was performed to determine feasibility/timing of testing and treatment assignment into 5 major molecular categories. **Results:** 50 GEC tumors had biomarker assessment and mock treatment assignment within 60 days, revealing HER2 (26%), MET (30%), FGFR2 (8%), EGFR (20%), KRAS/PI3K (26%). **Conclusions:** Comprehensive molecular profiling of FFPE tissue was feasible and timely. Tumors were classified into major molecular subgoups. PANGEA is a compromise between the number of potential treatment categories and feasibility of conducting such a trial.

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Cancro del colon-retto: qualche cosa cambia in incidenza?

Increasing disparities in age-related incidence of colon and rectal cancer in the United States, 1975-2010. *Presenting Author: Christina Edwards Bailey, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The overall incidence of colorectal cancer (CRC) has been decreasing since 1998, but there has been an apparent rise in the incidence of CRC in young adults. The primary aim of this study was to evaluate age-related disparities in secular trends in CRC incidence in the United States. **Methods:** A retrospective cohort study was performed using the Surveillance, Epidemiology, and End Results (SEER) registry. All patients diagnosed with colon or rectal cancer from 1975 to 2010 was queried. SEER*Stat (version 8.04, National Cancer Institute) was used to obtain the annual cancer incidence rates, annual percent change (APC), and corresponding p values for the secular trends. **Results:** Overall age-adjusted CRC incidence decreased by 0.92% between 1975 and 2010. There has been a steady decline in the incidence of CRC in patients age 50 years or older, but the opposite trend has been observed in patients 20 to 34 years of age. The APC for patients with localized, regional, and distant colon cancer at diagnosis in the 20 to 34 year age group was 1.10 (95% CI 0.28 to 1.93; $p=0.01$), 0.91 (95% CI 0.23 to 1.61; $p=0.01$) and 1.81 (95% CI 0.88 to 2.75; $p<0.001$). The APC for patients with localized, regional ,and distant rectal cancer in the 20 to 34 year age group was 4.03 (95% CI 3.02 to 5.05; $p<0.001$), 3.05 (95% CI 1.95 to 4.17; $p<0.001$) and 2.66 (95% CI 1.33 to 3.99; $p<0.001$). Based on current trends, in 2030 the incidence rate for colon and rectal cancer will increase by 90% and 124.2% respectively for patients 20 to 34 years of age while decreasing by 37.8% and 34.3% for patients 50 to 75 years of age. **Conclusions:** There has been a significant increase in the incidence of CRC diagnosed in patients age 20 to 34, with a decline in older patients. Further studies are needed to determine the cause for these trends and identify potential preventive and early detection strategies.

Percent change of APC-based predicted incidence rate of colon and rectal cancer by age compared to incidence rate in 2010.

	Colon		Rectal	
Age group	**2020**	**2030**	**2020**	**2030**
20-34	37.8%	90.0%	49.7%	124.2%
35-49	13.0%	27.7%	20.8%	46.0%
50-75	-21.2%	-37.8%	-19.0%	-34.3%
>75	-25.5%	-44.5%	-30.3%	-51.5%

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Cancro del colon-retto: la terapia con EGFR inibitori. Sempre più selezione

Analysis of *KRAS/NRAS* mutations in phase 3 study 20050181 of panitumumab (pmab) plus FOLFIRI versus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC). *Presenting Author: Marc Peeters, Department of Oncology, Antwerp University Hospital, Edegem, Belgium*

Background: Previously, this study showed significant improvement in progression-free survival (PFS) in pmab + FOLFIRI vs FOLFIRI (HR=0.73; 95% CI: 0.59-0.90; p=0.004) and a trend toward improved overall survival (OS; HR=0.85; 95% CI: 0.70-1.04; P=0.12; Peeters et al. JCO 2010). Recently, analysis from 1st-line mCRC PRIME study showed that mutations in *RAS* genes (*KRAS/NRAS* exons 2/3/4) predicted a lack of response to pmab (Douillard et al. NEJM 2013). **Methods:** The primary objective was to assess the tx effect of pmab + FOLFIRI vs FOLFIRI on OS and PFS based on *RAS* mutation status in the primary analysis population. Bidirectional Sanger sequencing was used to detect mutations in *KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4 in patients (pts) with known WT *KRAS* exon 2 mCRC. **Results:** In this prospective retrospective analysis, overall *RAS* ascertainment rate was 85% (n=1008/1186). 18% of the WT *KRAS* exon 2 pts harbored additional *RAS* mutations (n=107/597). Efficacy is shown (Table). Tx HR for pts with WT *RAS* was 0.803 (95% CI: 0.629-1.024; P=0.077) for OS and 0.695 (95% CI: 0.536-0.903; P=0.006) for PFS. **Conclusions:** Improvements were observed in the tx effect of pmab + FOLFIRI vs FOLFIRI on OS and PFS in the WT *RAS* group vs the WT *KRAS* exon 2 group. Pts with MT *RAS* mCRC are unlikely to benefit by the addition of pmab to FOLFIRI, similar to pts with MT *KRAS* exon 2 mCRC in this study. These findings are consistent with previously reported outcomes by *RAS* status and support *RAS* testing to determine potentially appropriate pts for pmab tx. Clinical trial information: NCT00339183.

	Pmab + FOLFIRI (N = 303)	FOLFIRI (N = 294)	HR (95% CI)	Descriptive p value
WT *RAS*,[a] n	204	211		
Median OS - mos	16.2	13.9	0.803	0.077
95% CI	14.5, 19.7	11.9, 16.1	0.629, 1.024	
Median PFS - mos	6.4	4.4	0.695	0.006
95% CI	5.5, 7.4	3.7, 5.5	0.536, 0.903	
MT *RAS*,[b] n	299	294		
Median OS - mos	11.8	11.1	0.914	0.345
95% CI	10.4, 13.1	10.2, 12.4	0.759, 1.101	
Median PFS - mos	4.8	4.0	0.861	0.144
95% CI	3.7, 5.5	3.6, 5.5	0.705, 1.053	
WT *KRAS* exon 2 MT *RAS*,[c] n	61	46		
Median OS - mos	11.3	9.2	0.825	0.402
95% CI	8.3, 13.1	7.0, 12.9	0.527, 1.293	
Median PFS - mos	3.7	3.7	0.892	0.627
95% CI	2.3, 5.8	2.8, 5.1	0.561, 1.419	

[a] WT in *KRAS* and *NRAS* exons 2, 3, and 4. [b] MT in any *KRAS* or *NRAS* exon 2, 3, or 4. [c] MT in *KRAS* exon 3 or 4 or *NRAS* exon 2, 3, or 4.

2014 Gastrointestinal Cancers Symposium

Cancro del colon-retto: la terapia con EGFR inibitori. Sempre più selezione

Effect of *KRAS* and *NRAS* mutations on treatment outcomes in patients with metastatic colorectal cancer (mCRC) treated first-line with cetuximab plus FOLFOX4: New results from the OPUS study. *Presenting Author: Sabine Tejpar, Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium*

Background: Patients with *KRAS* exon 2 codon 12/13 wild-type (wt) mCRC benefit significantly from the addition of cetuximab to first-line FOLFOX4 in relation to response and progression-free survival. Patients with *KRAS* exon 2 codon 12/13 mutations show no benefit with a trend to worse clinical outcomes. **Methods:** Tumors from OPUS study patients previously defined as *KRAS* codon 12/13 wt (n=179) were screened for specific mutations in *KRAS* exons 3 and 4 (8) and *NRAS* exons 2, 3, and 4 (18) using BEAMing technology. Treatment outcomes were assessed according to mutation status. **Results:** *RAS* tumor mutation status was evaluable for 118/179 (66%) patients. Mutations at the screened loci were detected in 36 (31%) patients. In the *RAS* wt population, there was benefit associated with the addition of cetuximab to FOLFOX4 (Table). In the overall *RAS*-mutant population, there was less favorable clinical outcome and no benefit from the addition of cetuximab to FOLFOX4. **Conclusions:** Patients with mCRC harboring any activating mutation of *KRAS* or *NRAS* are unlikely to benefit from the addition of cetuximab to FOLFOX4. Definitive conclusions for patients with new tumor mutations cannot be drawn due to low patient numbers. Restricting cetuximab administration to patients with tumors wt at all such loci might enable the further tailoring of therapy to maximize patient benefit.

	RAS wt† (all tested loci)		New *RAS* mt†		*RAS* mt‡ (any tested locus)	
	FOLFOX4 + cet	FOLFOX4	FOLFOX4 + cet	FOLFOX4	FOLFOX4 + cet	FOLFOX4
Parameter	N=36	N=46	N=17	N=19	N=94	N=78
Response rate, %	61.1	30.4	47.1	36.8	36.2	48.7
Odds ratio	3.46		1.50		0.61	
95% CI	1.37–8.71		0.38–5.95		0.33–1.12	
p-value*	0.008		0.57		0.11	
Median PFS, months	12.0	5.8	7.3	7.4	5.6	7.8
HR	0.43		1.02		1.59	
95% CI	0.21–0.88		0.41–2.55		1.08–2.36	
p value**	0.018		0.96		0.018	
Median OS, months	20.7	17.8	14.8	17.8	13.4	17.8
HR	0.83		1.41		1.35	
95% CI	0.49–1.41		0.62–3.21		0.95–1.92	
p value**	0.50		0.41		0.089	

†*RAS* evaluable population (n=118). ‡ Subset of the *KRAS* evaluable biomarkers population (n=315). * Cochran-Mantel-Haenszel. ** Log rank. Abbreviations: cet, cetuximab; HR, hazard ratio; mt, mutant; OS, overall survival; PFS, progression-free survival.

2014 Gastrointestinal Cancers Symposium

Cancro del colon-retto: la terapia con EGFR inibitori. Sempre più selezione

Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. *Presenting Author: Sebastian Stintzing, Department of Hematology and Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, LMU Munich, Munich, Germany*

Background: The FIRE-3 study (AIO KRK-0306) was designed as a randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab (cet) to FOLFIRI plus bevacizumab (bev) as first-line treatment in KRAS WT mCRC patients. FOLFIRI plus cet as first-line treatment of KRAS WT mCRC patients resulted in comparable overall response rates (ORR) and progression free survival (PFS) when compared to FOLFIRI plus bev. Overall survival (OS) was significantly longer in the FOLFIRI plus cet arm. **Methods:** In a preplanned analysis, the effect of mutations within the EGFR dependent pathway were investigated. Next to mutations within KRAS (exon 2, 3, 4), NRAS (exon 2, 3, 4) and BRAF (V600E), mutations within PIK3CA (exon 9 and 20) and Akt were investigated and their impact on ORR, PFS and OS within the FIRE-3 population was evaluated. The analysis of all mutations was carried out employing pyrosequencing. **Results:** The ITT population consisted of 592 KRAS WT (exon 2) patients. The current analysis includes 488 cases (82.4%) with tumor tissue available. In 407 pts sequencing of all RAS mutations was possible. The ORR within the WT RAS patient group was higher in the FOLFIRI plus cet arm (65.5% vs 59.6%; Fisher´s p: 0.157). HRs (cet; bev) for pts with WT *RAS*were 0.93 (95% CI, 0.74-1.17; p = 0.54) for PFS and 0.70 (95% CI, 0.53-0.92; p = 0.01) for OS. PIK3CA mutation did not influence PFS nor OS when compared to the RAS wt population. **Conclusions:** ORR and OS were increased in patients with cet plus FOLFIRI as compared to bev plus FOLFIRI in patients without RAS mutations. Exclusion of patients with RAS mutations identifies a population which is more likely to benefit from cetuximab. Clinical trial information: NCT00433927.

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Cancro del colon-retto: la ricerca italiana

Early tumor shrinkage (ETS) and deepness of response (DoR) to predict progression-free, postprogression, and overall survival: Results from the phase III TRIBE trial. *Presenting Author: Chiara Cremolini, U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy*

Background: The TRIBE trial demonstrated that first-line FOLFOXIRI plus bevacizumab (bev) improves PFS, response rate (RECIST), and OS in comparison to FOLFIRI plus bev (ASCO Annual Meeting 2013). Recent experiences evidenced that both ETS and DoR may implement the assessment of response and correlate with survival in metastatic colorectal cancer (mCRC). **Methods:** ETS was defined as the relative change in the sum of longest diameters of RECIST target lesions at week 8 compared to baseline. A 20% decrease was adopted as cut-off value to discriminate early responders and non-responders. DoR was defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir in the absence of new lesions or progression of non-target lesions compared to baseline. The median value was used as cut-off. **Results:** Out of 508 randomized patients, 443 and 484 patients were evaluable for ETS and DoR, respectively. Early responders achieved longer PFS (median PFS: 12.7 vs 10.0 mos, HR: 0.66 [0.52-0.79], $p<0.0001$), post-progression survival (median PPS: 17.1 vs 10.7 mos, HR: 0.64 [0.47-0.81], $p=0.0005$) and OS (median OS: 35.8 vs 22.4 mos, HR: 0.54 [0.39-0.67], $p<0.0001$). Patients achieving a DoR higher than the median reported longer PFS (median PFS: 13.1 vs 9.3 mos, HR: 0.61 [0.49-0.73], $p<0.0001$), PPS (median PPS: 18.4 vs 10.5 mos, HR: 0.58 [0.44-0.73], $p<0.0001$) and OS (median OS: 36.8 vs 21.3 mos, HR: 0.47 [0.35-0.58], $p<0.0001$). A significant correlation of DoR as a continuous variable with PFS (HR: 0.983 [0.979-0.986], $p<0.0001$), PPS (HR: 0.987 [0.984-0.991], $p<0.0001$) and OS (HR: 0.979 [0.975-0.983], $p<0.0001$) was observed. No differences across arms were reported. **Conclusions:** ETS and DoR predict PFS, PPS and OS. These findings support the hypothesis that the adoption of active upfront regimens, able to induce a rapid and deep tumor shrinkage, may positively affect the subsequent disease history, thus translating into an advantage in survival. Clinical trial information: NCT00719797.

LDH serum levels as a predictive factor for global outcome in pretreated colorectal cancer patients receiving regorafenib: Implications for clinical management. *Presenting Author: Michela Del Prete, Medical Oncology - AOU Ospedali Riuniti Università Politecnica delle Marche, Ancona, Italy*

Background: Although a demonstrated clinical efficacy, a non negligible proportion of colorectal cancer patients does not seem to benefit from regorafenib and are consequently exposed to unnecessary toxicity. LDH serum levels represent an indirect marker of tumour hypoxia, neo-angiogenesis and worse prognosis in many tumour types. In colorectal cancer LDH showed a correlation with treatment outcome for patients receiving antiangiogenetic treatment, thus suggesting a possible interaction with the activity profile of these drugs. We analyzed the role of LDH serum levels in predicting clinical outcome for pre-treated metastatic colorectal cancer patients receiving regorafenib. The final aim was to individuate a potentially reliable and easy to use marker for patients stratification. **Methods:** 118 colorectal cancer patients treated with regorafenib were available for our analysis. For all patients, LDH values were collected within one month before the procedure and after treatment end. LDH cutoff value was determined by ROC curve analysis, patients were then divided into two groups (A and B, below and above cut-off level respectively). Patients were also classified according to the variation in LDH serum levels pre- and post-treatment (increased patients vs. decreased patients). **Results:** Patients in group A and B proved homogeneous for all clinical characteristics analyzed. In group A patients median progression free survival (PFS) was 3.18 months, whereas it was 1.87 months in group B patients ($p = 0.0018$). Median overall survival (OS) was 6.23 months and 3.28 months in group A and B respectively ($p = 0.048$). Significant differences were not noted among the 2 groups for response rate. All the other clinical variables analyzed failed to show any correlation with patients outcome. **Conclusions:** Our observations seem to suggest a role of LDH as a marker of clinical outcome in colorectal cancer patients receiving regorafenib. We can then speculate that high LDH patients may not be optimal candidates for regorafenib. After further confirmation in larger trial, these findings may be relevant for a better patients stratification and selection.