MADRID 2014 ESMO congress

TTD Contribution to the Precision Oncology

Dr. Enrique Aranda. Chairman
Spanish Cooperative Group for Digestive Tumour Therapy

DISCLOSURE SLIDE

- Advisory role: Amgen, Bayer, Celgene, Merk, Roche, Sanofi

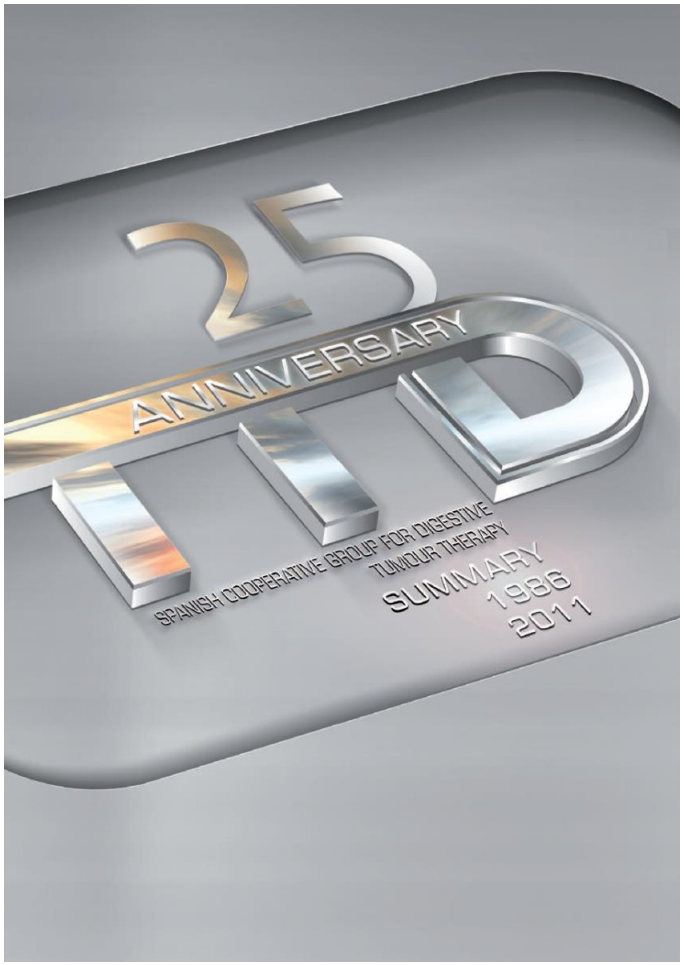
History and objectives

History

The Spanish Cooperative Group for Digestive Tumour Therapy, has been working in the design and development of protocols in the field of gastrointestinal tumours since 1986.

Objectives

- Develop clinical research protocols
- Introduce quality into healthcare through the improved oncological training of its members.
- Work at the heart of a cooperative group.
- Publish work on the studies performed to create an international impact



Activities

Research Activity

- Clinical research
- Translational research

Educational and Training Activity

- International and National meetings
- Consensus documents
- Events sponsoring
- Collaboration with patient associations

The TTD Group in figures

298 members | **139 hospitals**

Research Activity:

- Clinical: 1986-2014
  - Nº studies: 83
  - Nº patients*: 10.173
- Basic: 2008-2014 (n=2.455)
- Publications:
  - Journals: 75
  - Conferences: 167

Educational and Training Activity:

- Consensus documents : 8
  - **2006: Adjuvant treat. colon Ca.**
  - **2007: Colorectal Ca. liver Mets.**
  - **2009: Gastric Ca.**
  - **2010: Hereditary colorectal Ca.**
  - **2011: Metastatic colorectal Ca.**
  - **2012: Hereditary pancreatic Ca.**
  - **2013: Peritoneal Carcinomatosis**
  - **2013: Exocrine pancreas**
- Sponsorship of scientific activities (2006-2013): 60
- International meetings: 22
- Collaboration with patients' associations : Europacolon

* 1.547 retrospective series

TTD CONTRIBUTION

5-FU

5-FU: 20 years of research

1990: Díaz-Rubio E. Phase I-II 5FU IC 48h in mCRC. Eur J Cancer. 26(6):727-9.
1994: Díaz-Rubio E. Phase II 5FU IC 48h in mCRC. J Infusional Chemoth. 4 (1): 58-61
1995: Aranda E. Phase II 5FU IC(3 gr/m^2) 48h+oral LV in mCRC. Cancer. 15;76(4):559-63.
1996: Aranda E. Phase II 5FU IC(2 gr/m^2) 48h+oral LV in mCRC. Ann Oncol. 7(6):581-5.
1998: Aranda E. Phase III LV+5FU bolus vs 5FU IC 48h in mCRC. Ann Oncol. 9(7):727-31.
2002: Kohne CH. Clinical determinants of survival in pts with 5-FU for mCRC: multivariante analysis of 3825 pts. Ann Oncol. 13 (2):308-17
2004: Folprecht G. Efficacy of 5-FU-based QT in elderly pts with mCRC: a pooled analysis of clinical trials. Ann Oncol. 15(9):1330-8
2004: Aranda E. Phase I/II irinotecan+5FU IC48h in mCRC. Ann Oncol. 15(4):559-67.
2005: Sastre J. Phase II irinotecan+5FU IC48h for elderly pts in mCRC. J Clin Oncol. 23(15):3545-51
2005: Abad A. Phase II oxaliplatin+5FU IC 48h in mCRC. Clin. Colorectal Cancer. Mar;4(6):384-9
2007: Díaz-Rubio E. Phase III XELOX vs FUOX in mCRC. J Clin Oncol. 25(27):4224-30
2008: Abad A. Phase II FUOXIRI in mCRC. Acta Oncol. 2008;47:286-292
2009: Sastre J. Elderly pts: comparative outcomes from the 03-TTD-01 phase III study. Crit Rev Oncol Hematol. 70(2), Pg 134-144.
2009: Aranda E. Phase III FUIRI vs FOLFIRI in mCRC. Annals of Oncology. 2009 Feb;20(2):251-7
2010: E. Martinez-Balibrea, et al. UGT1A and TYMS genetic variants are predictive for toxicity and response in CCR pts treated with first-line irinotecan and fluorouracil combination therapy. Br J Cancer. 2010 Aug 10;103(4):581-9.

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Macro Study

The Oncologist®

Academia–Pharma Intersect: Gastrointestinal Cancer

First-Line XELOX Plus Bevacizumab Followed by XELOX Plus Bevacizumab or Single-Agent Bevacizumab as Maintenance Therapy in Patients with Metastatic Colorectal Cancer: The Phase III MACRO TTD Study

EDUARDO DÍAZ-RUBIO,[a] AUXILIADORA GÓMEZ-ESPAÑA,[b] BARTOMEU MASSUTÍ,[c] JAVIER SASTRE,[a] ALBERT ABAD,[d] MANUEL VALLADARES,[e] FERNANDO RIVERA,[f] MARIA J. SAFONT,[g] PURIFICACIÓN MARTÍNEZ DE PRADO,[h] MANUEL GALLÉN,[i] ENCARNACIÓN GONZÁLEZ,[j] EUGENIO MARCUELLO,[k] MANUEL BENAVIDES,[l] CARLOS FERNÁNDEZ-MARTOS,[m] FERRÁN LOSA,[n] PILAR ESCUDERO,[o] ANTONIO ARRIVI,[p] ANDRÉS CERVANTES,[q] ROSARIO DUEÑAS,[r] AMELIA LÓPEZ-LADRÓN,[s] ADELAIDA LACASTA,[t] MARTA LLANOS,[u] JOSE M. TABERNERO,[v] ANTONIO ANTÓN,[w] ENRIQUE ARANDA,[b] **on behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)**

The Oncologist 2012;17:15–25 www.TheOncologist.com

Summary of efficacy

	XELOX-BEV (N=239)	s/a BEV (N=241)	HR (95% CI)
PFS median Events %	10.4 (9.3-12.0) 72%	9.7 (8.3-10.6) 76%	1.098 (0.89–1.35)
OS median Events %	23.2 (20.0-26.0) 73%	20.0 (17.1-23.3) 72%	1.05 (0.85–1.30)
Confirmed OR %	47%	49%	0.95 (0.66-1.36)*

*Odds Ratio

Conclusions

- The results from this study indicate that noninferiority in terms of the PFS interval cannot be confirmed for single-agent bevacizumab maintenance compared with XELOX plus bevacizumab maintenance after induction therapy with six cycles of XELOXplus bevacizumab, because the upper limit of the 95%CI was greater than the prespecified limit of 1.32. However, a detriment in the median PFS duration of 3 weeks can be excluded.

- This study suggests that maintenance strategy with single-agent bevacizumab after induction with XELOX plus bevacizumab for six cycles may be a valid option in this setting, without compromising the PFS interval, OS time, RR, duration of response, or surgical treatment of metastases, with an important lower incidence of certain toxicities, such as neuropathy, hand–foot syndrome, and fatigue.

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Macro Study CTC

The Oncologist®

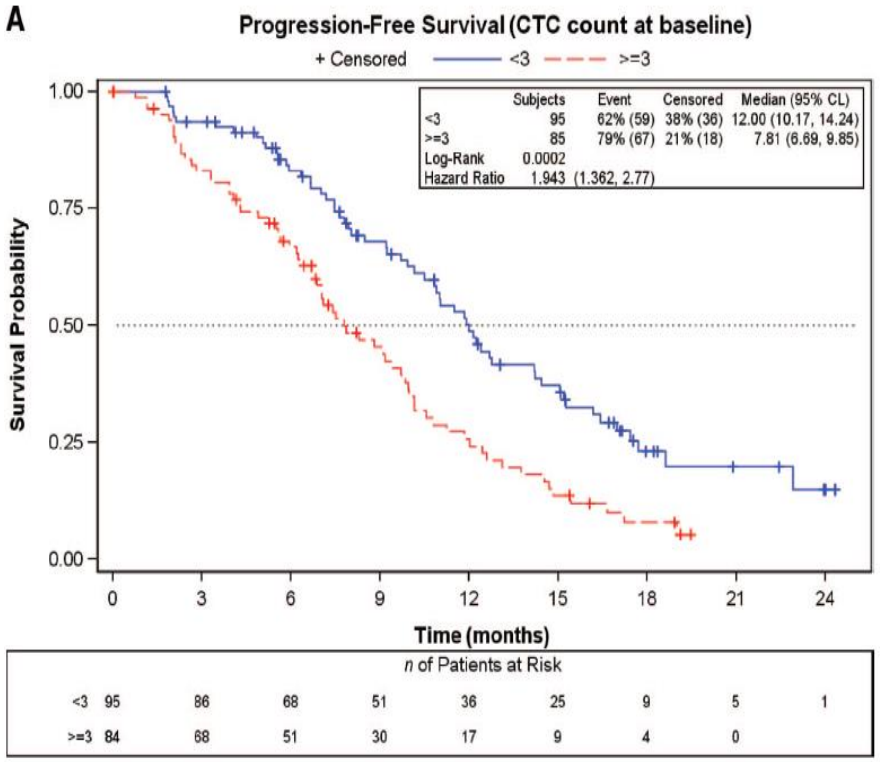
Gastrointestinal Cancer

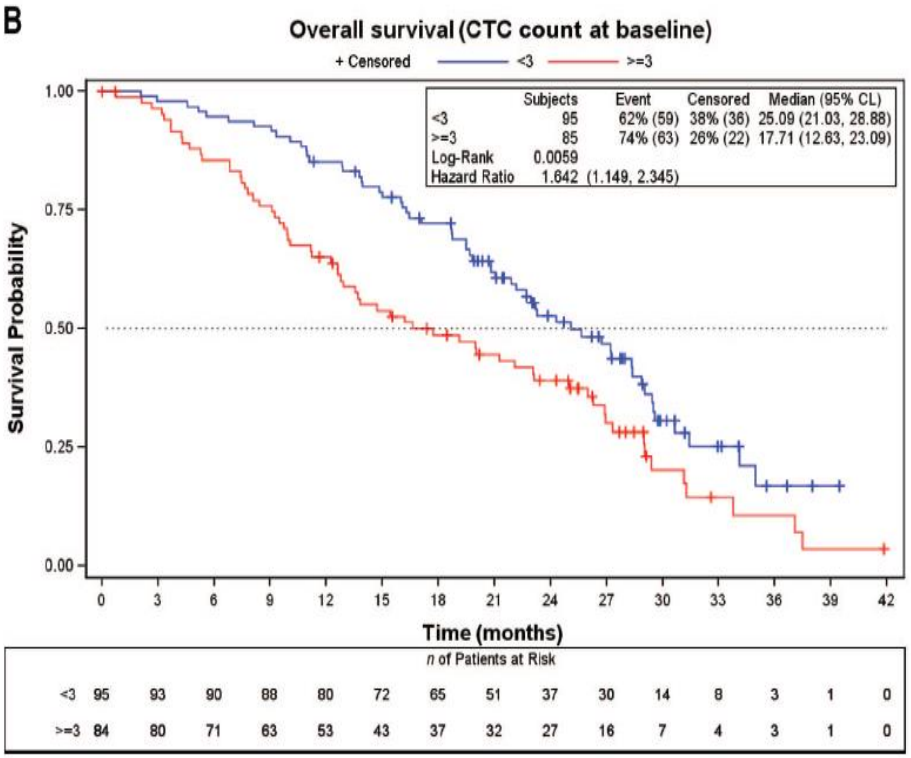
Circulating Tumor Cell Count Is a Prognostic Factor in Metastatic Colorectal Cancer Patients Receiving First-Line Chemotherapy Plus Bevacizumab: A Spanish Cooperative Group for the Treatment of Digestive Tumors Study

JAVIER SASTRE,[a] M. LUISA MAESTRO,[b] AUXILIADORA GÓMEZ-ESPAÑA,[c] FERNANDO RIVERA,[d] MANUEL VALLADARES,[e] BARTOMEU MASSUTI,[f] MANUEL BENAVIDES,[g] MANUEL GALLÉN,[h] EUGENIO MARCUELLO,[i] ALBERT ABAD,[j] ANTONIO ARRIVI,[k] CARLOS FERNÁNDEZ-MARTOS,[l] ENCARNACIÓN GONZÁLEZ,[m] JOSEP M. TABERNERO,[n] MARTA VIDAURRETA,[b] ENRIQUE ARANDA,[c] EDUARDO DÍAZ-RUBIO[a]

The Oncologist 2012;17:947–955 www.TheOncologist.com

Progression free survival and overall survival according CTC count at baseline





Response rate and PFS and OS times at baseline and at cycle 3

Table 2. Response rate and PFS and OS times

	CTC count at cycle 3			CTC count at baseline		
Outcome	**<3**	**≥3**	***p*-value**	**<3**	**≥3**	***p*-value**
Response rate	53.2%	26.1%	.0168	48.4%	40.0%	.2563
	OR, 3.22 (95% CI, 1.25–9.43)			OR, 1.4 (95% CI, 0.78–2.55)		
Median PFS, mos	10.8	7.5	.005	12.0	7.8	.0002
	HR, 2.06 (95% CI, 1.23–3.46)			HR, 1.94 (95% CI, 1.36–2.77)		
Median OS, mos	25.1	16.2	.0095	25.1	17.7	.0059
	HR, 1.96 (95% CI, 1.17–3.30)			HR, 1.64 (95% CI, 1.15–2.35)		

Abbreviations: CI, confidence interval; CTC, circulating tumor cell; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival.

Conclusions

- These results confirm that the CTC count at baseline is a strong prognostic factor for PFS and OS outcomes in patients with metastatic colorectal cancer and it would be of interest to implement this test in clinical practice.
- These findings are in line with results from the CAIRO2 trial, which suggested a correlation between CTC and survival in patients with mCRC.
- Future studies in patients with mCRC should include assessment of CTCs at baseline and during therapy.

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Macro Study Kras

OPEN ACCESS Freely available online

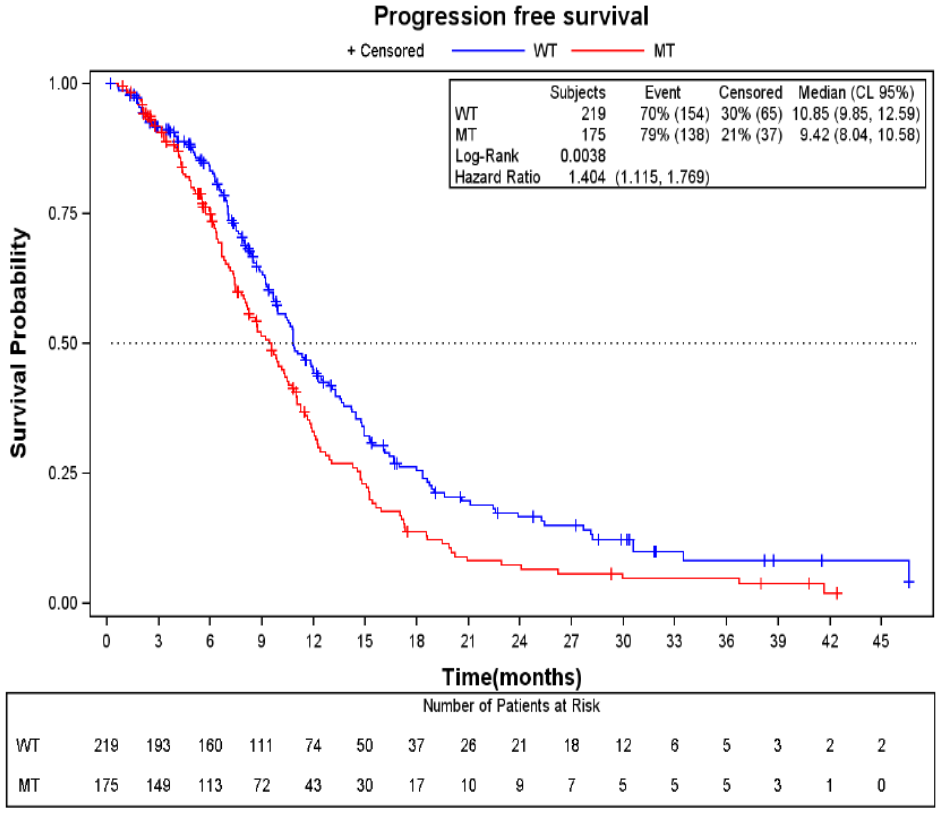
PLOS ONE

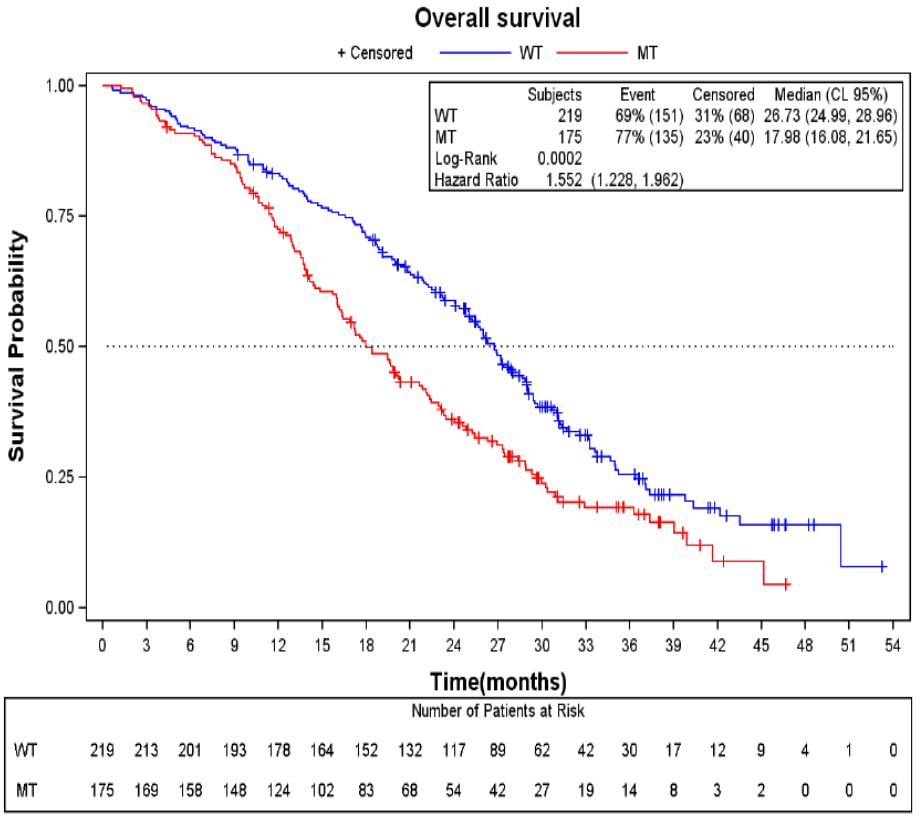
Role of Kras Status in Patients with Metastatic Colorectal Cancer Receiving First-Line Chemotherapy plus Bevacizumab: A TTD Group Cooperative Study

Eduardo Díaz-Rubio[1]*, Auxiliadora Gómez-España[2], Bartomeu Massutí[3], Javier Sastre[1], Margarita Reboredo[4], José Luis Manzano[5], Fernando Rivera[6], Mª José Safont[7], Clara Montagut[8], Encarnación González[9], Manuel Benavides[10], Eugenio Marcuello[11], Andrés Cervantes[12], Purificación Martínez de Prado[13], Carlos Fernández-Martos[14], Antonio Arrivi[15], Inmaculada Bando[1], Enrique Aranda[2] on behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)[¶]

PLOS ONE | www.plosone.org October 2012 | Volume 7 | Issue 10 | e47345

Progression free survival and overall survival according KRAS status





Conclusions

- This analysis of the MACRO study suggests a prognostic role for tumour KRAS status in patients with mCRC treated with XELOX plus bevacizumab. For both PFS and OS, KRAS status was an independent factor in univariate and multivariate analyses.

Macro Study CTC + KRAS

Original Study

Prognostic Value of the Combination of Circulating Tumor Cells Plus *KRAS* in Patients With Metastatic Colorectal Cancer Treated With Chemotherapy Plus Bevacizumab

Javier Sastre,[1] Marta Vidaurreta,[2] Auxiliadora Gómez,[3] Fernando Rivera,[4] Bartomeu Massutí,[5] Margarita Reboredo López,[6] Albert Abad,[7] Manuel Gallen,[8] Manuel Benavides,[9] Enrique Aranda,[3] Eduardo Díaz Rubio,[1] for the Spanish Cooperative Group for the Treatment of Digestive Tumors

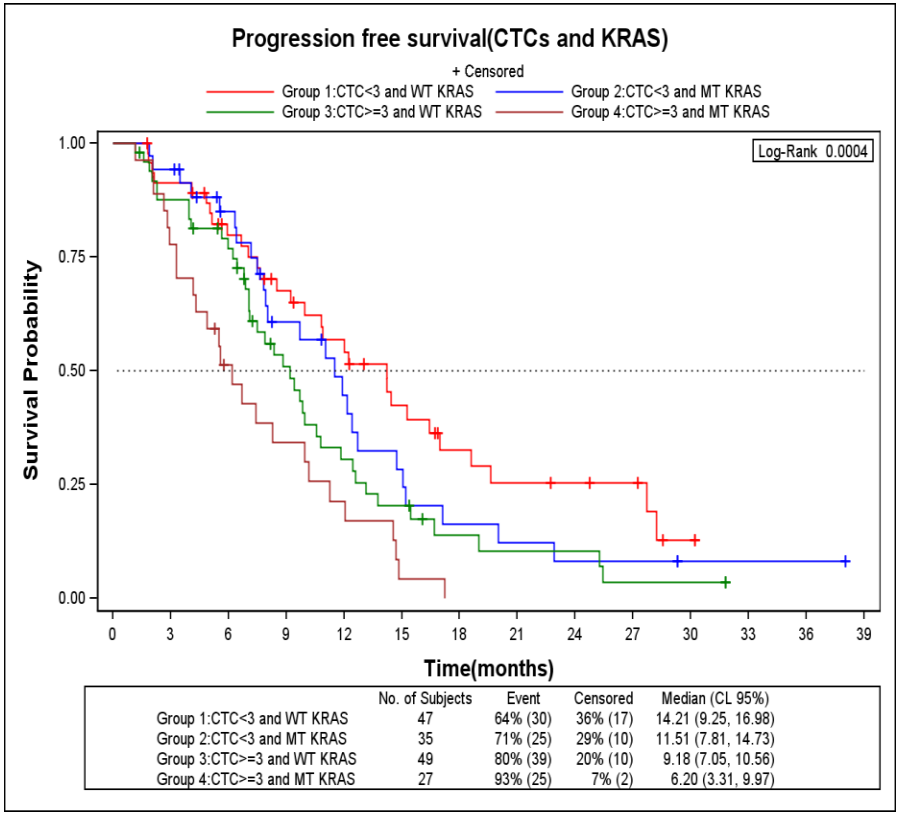
Abstract

This is a post hoc analysis of biomarkers from a phase III clinical trial in metastatic colorectal cancer. Circulating tumor cell count and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog status were the strongest independent factors for progression-free and overall survivals. Selection of high- and low-risk populations may help to individualize approaches in the future.

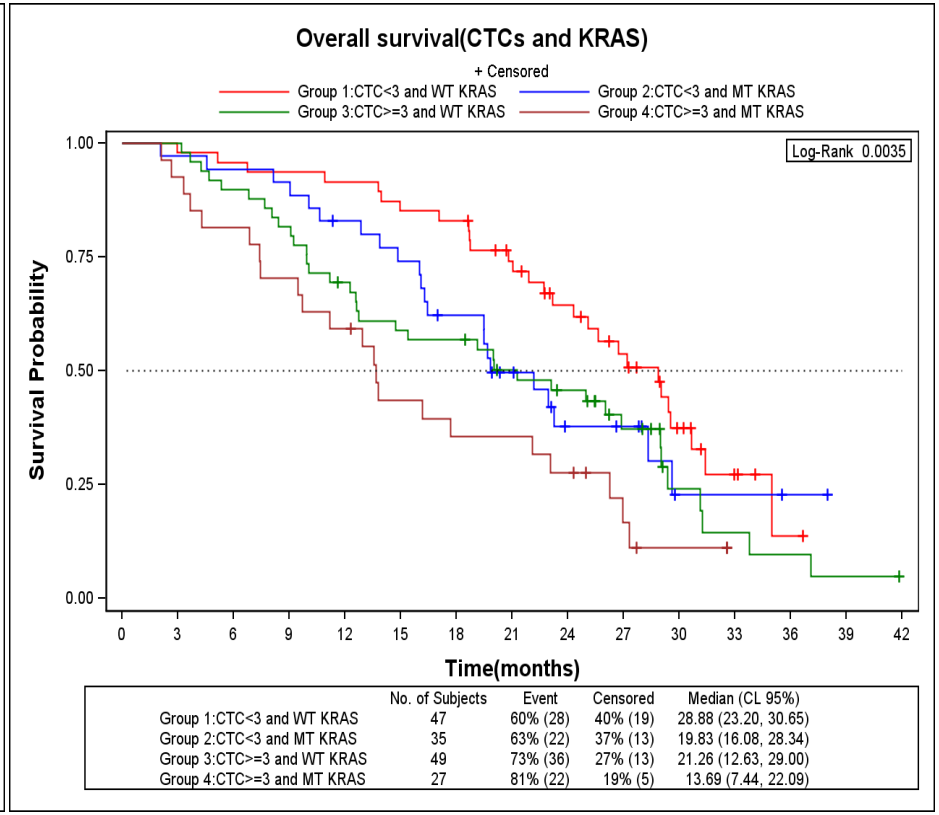
Objective: Circulating tumor cells (CTCs) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) status were identified as prognostic factors for progression-free survival (PFS) and overall survival (OS) in patients with metastatic colorectal cancer treated with chemotherapy and bevacizumab in analyses of the MACRO (Maintenance Treatment in Advanced Colorectal Cancer) trial. In this post hoc analysis of the MACRO trial, the potential additive effect of these 2 factors on patient outcomes was explored. **Methods:** A total of 158 of the 480 patients involved in the MACRO trial were included in the biological marker substudy. CTC isolation and enumeration were centralized and performed using the CellSearch System (Veridex LLC, Raritan, NJ) in 7.5 mL of whole blood. Evaluation of *KRAS* status was performed retrospectively by the standard method used at each center. PFS and OS were analyzed by the Kaplan–Meier method according to CTC count and *KRAS* status. **Results:** Patients with < 3 CTC per 7.5 mL blood at baseline and *KRAS* wild-type tumors had a median PFS of 14.2 months compared with 6.2 months in patients with ≥ 3 CTCs and *KRAS* mutated tumors ($P < .0001$; hazard ratio, 3.0; 95% confidence interval, 1.8-5.2). Similar findings were observed for OS (28.9 and 13.7 months, respectively, $P = .0004$; hazard ratio 2.8; 95% confidence interval, 1.6-4.9). Multivariate analyses showed that CTC count ≥ 3 and *KRAS* status were the only independent prognostic factors for both PFS and OS. **Conclusions:** This post hoc analysis showed that CTC count and *KRAS* status were independent prognostic factors for outcomes in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy. These factors should be taken into account in the design of future phase III trials.

Clinical Colorectal Cancer, Vol. 12, No. 4, 280-6
Keywords: Bevacizumab, Capecitabine, Circulating tumor cells, Colorectal cancer, *KRAS* status, Oxaliplatin Prognostic factors

Progression free survival and overall survival according to baseline CTC and KRAS status



	No. of Subjects	Event	Censored	Median (CL 95%)
Group 1:CTC<3 and WT KRAS	47	64% (30)	36% (17)	14.21 (9.25, 16.98)
Group 2:CTC<3 and MT KRAS	35	71% (25)	29% (10)	11.51 (7.81, 14.73)
Group 3:CTC>=3 and WT KRAS	49	80% (39)	20% (10)	9.18 (7.05, 10.56)
Group 4:CTC>=3 and MT KRAS	27	93% (25)	7% (2)	6.20 (3.31, 9.97)



	No. of Subjects	Event	Censored	Median (CL 95%)
Group 1:CTC<3 and WT KRAS	47	60% (28)	40% (19)	28.88 (23.20, 30.65)
Group 2:CTC<3 and MT KRAS	35	63% (22)	37% (13)	19.83 (16.08, 28.34)
Group 3:CTC>=3 and WT KRAS	49	73% (36)	27% (13)	21.26 (12.63, 29.00)
Group 4:CTC>=3 and MT KRAS	27	81% (22)	19% (5)	13.69 (7.44, 22.09)

KRAS-CTCs based Risk profiles

Risk profile (Prevalence rate %) PFS=Median months (2 year PFS rate %) OS=Median months (2 year survival rate %)		CTCs		N=155
		<3	≥ 3	
KRAS	Wild type	Low (28%) PFS= 14.2(27%) OS= 28.9(64%)	Medium(30%) PFS= 9.2(11%) OS= 23.1(48%)	WT (59%) PFS= 10.8(18%) OS= 26.0(56%)
	Mutated	Medium (24%) PFS= 11.5(8%) OS= 19.8(39%)	High (17%) PFS= 6.2(0%) OS= 13.6(24%)	MT (41%) PFS= 8.0(4%) OS= 18.7(32%)
		CTC <3 (52%) PFS= 12.2(18%) OS= 25.1(53%)	CTC ≥3 (48%) PFS=7.9(7%) OS= 17.7(39%)	Total 155 PFS= 9.9(12%) OS= 23(46%)

Low Risk | Medium Risk | High Risk

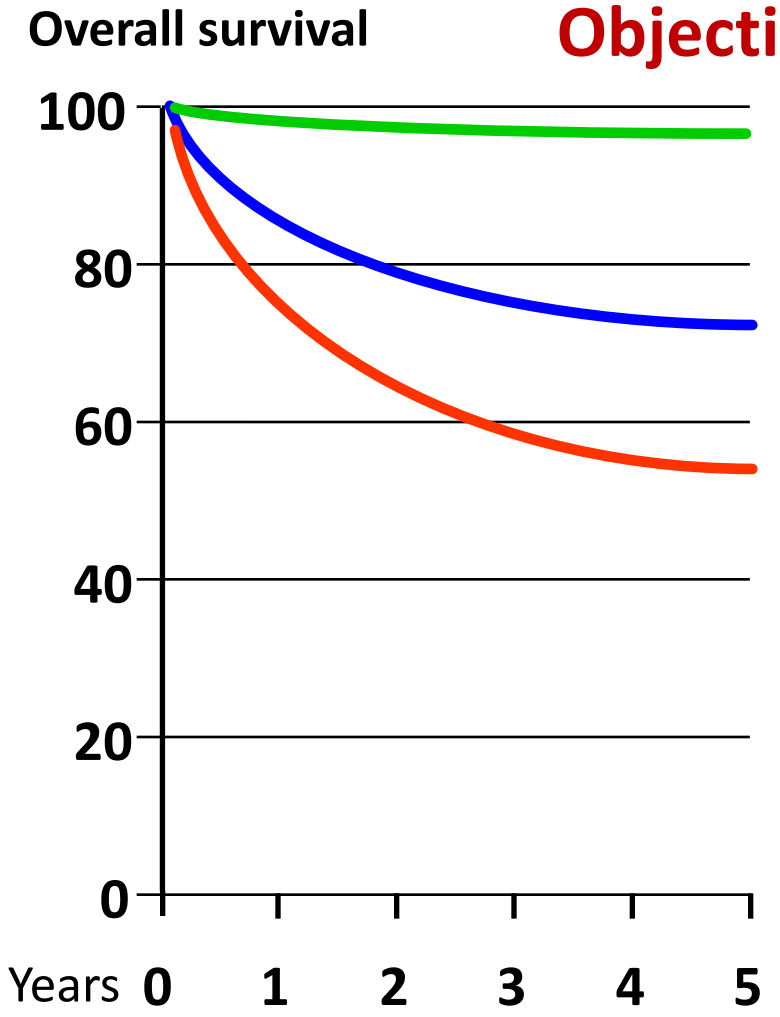
Conclusions

- This post-hoc analysis showed that CTC count and KRAS status were independent prognostic factors for outcomes in patients with metastatic colorectal cancer treated with bevacizumab ± chemotherapy.
- Baseline CTC count and KRAS status can be used in combination to select different subgroups of patients (i.e. low, intermediate and high risk).
- These factors should be taken into account in the design of future phase III trials.

Adjuvant Chemotherapy in Colon Cancer

TTD-RTICC (2009): 500 pts

Objectives of the study (III + FOLFOX)



Good prognosis

All pts

Bad prognosis

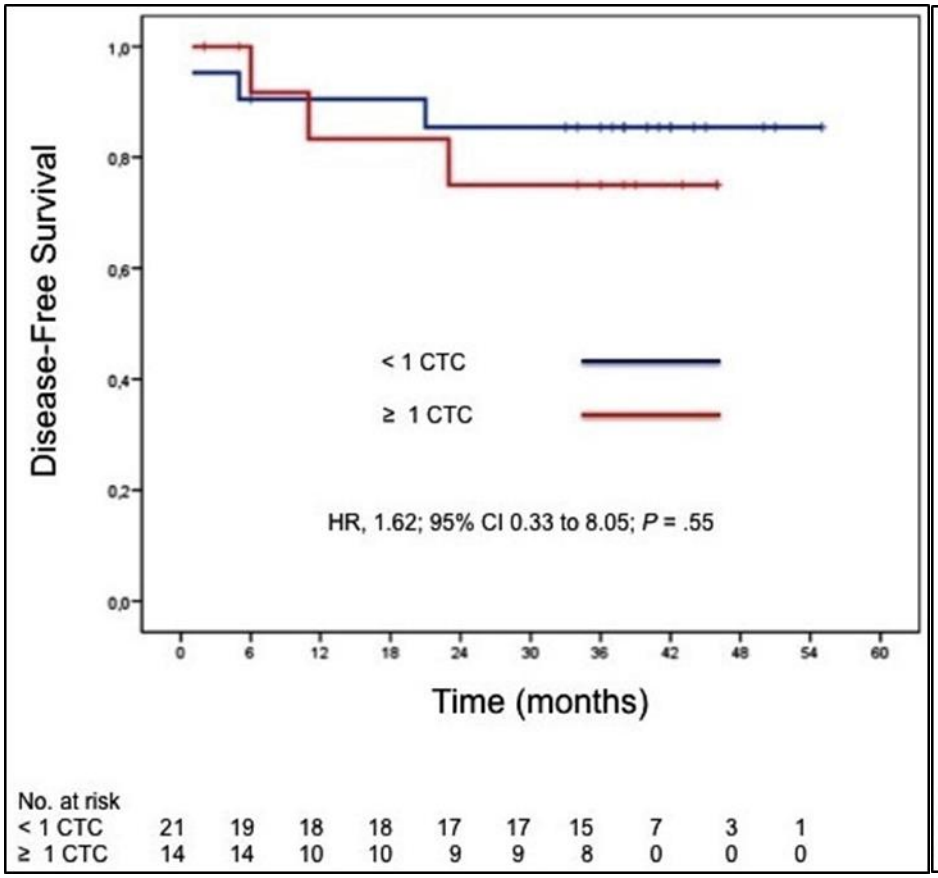
MARKERS

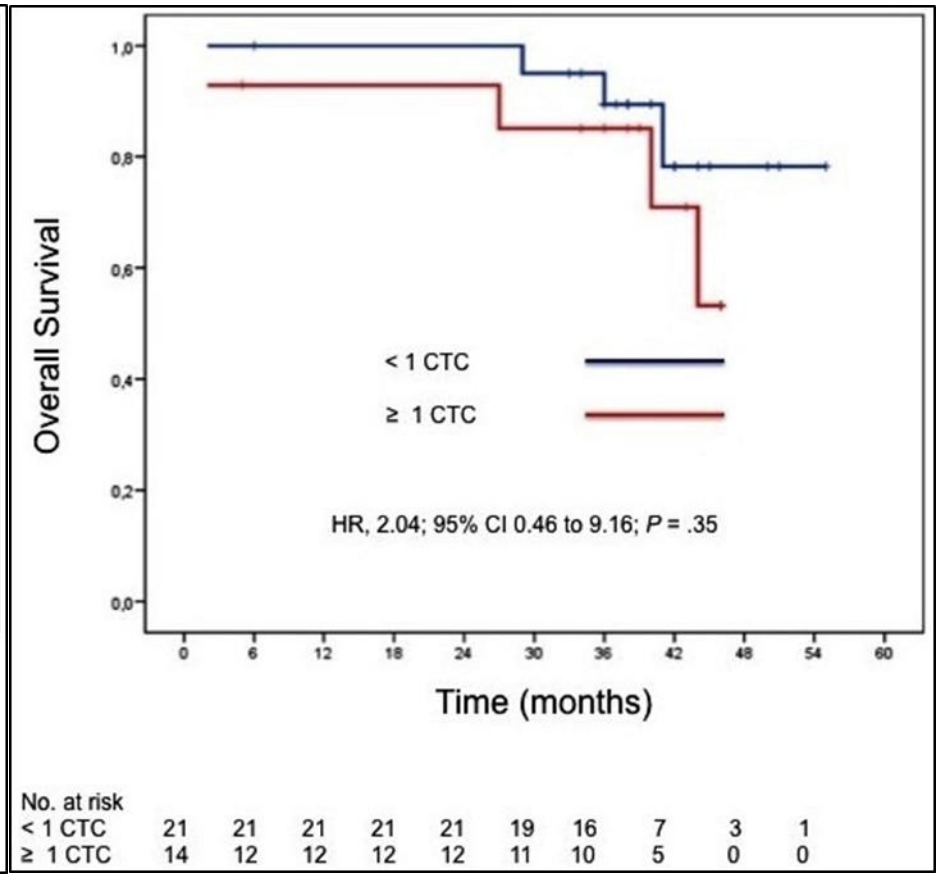
- CTC
- KRAS
- BRAF
- MSI
- microRNAs

Good Signature (Good prognosis)

Bad signature Bad prognosis)

DFS and OS in patients with stage IIIA CRC according to CTC count using the cutoff-point of 1 CTC





Conclusions

- CTC presence was more frequent in patients with higher risk of relapse.
- CTC detection was not associated with worse DFS and OS in the overall population, although it might be associated with an increased risk of relapse and death in patients with stage IIIA CC. However, a longer follow-up is needed.
- We suggest CTC ≥ 1 as the optimal cutoff to be used in future studies in the adjuvant setting of CRC

TTD Contribution

Recent:

The circulating tumor cell (CTC) count as a prognostic and/or predictive marker for efficacy endpoints

- CTC and KRAS (mCRC treated with bevacizumab+QT): MACRO1 study
- CTC (resected CRC): RETICC study

TTD recruiting and follow up studies

TRIAL	PHASE	STATUS	CASES
Metastatic colon			
mFOLFOX+Cmab vs mFOLFOX x8 ->Cmab(MACRO-2)	II	FOLLOW-UP	193
XELOX+Bev vs QT personalized+Bev (SETICC)	II	FOLLOW-UP	195
QT (RP/EE) -> axitinib/placebo	II	OPEN	42
CTC ≥ 3: FOLFOX+Bev vs FOLFOXIRI+Bev(VISNÚ-1)	III	OPEN	162
CTC < 3 and BRAF/PI3K status:FOLFIRI+Bev vs FOLFIRI+Cmab (VISNÚ-2)	II	OPEN	92
KRAS,BRAF, NRAS, PI3K status FOLFIRI+Pmab (ULTRA)	II	OPEN	43
LIVER ONLY METASTASES			
FOLFOX+Pmab vs FOLFIRI+Pmab (mt hp) (PLANET)	II	FOLLOW-UP	80
FRAIL AND/OR UNFIT FOR QT			
Pmab >70 years suboptimal (FRAIL)	II	FOLLOW-UP	33
Regorafenib (REFRAME)	II	OPEN	23
RECTAL			
XEL + RT ± Bev (rectal) (AVAXEL)	II	FOLLOW-UP	90
SECOND AND SUBSEQUENT LINES			
Regorafenib in RAS/BRAF previously treated FOLFOXIRI+bev (PREVIUM)	II	OPEN	-
CPT-11+Pmab (failure CPT-11) (SPECTRA)	II	FOLLOW-UP	61
Adjuvant colon			
CTC	-	FOLLOW-UP	519
FOLFOX4 ± Cmab (PETACC-8)*	ADY	FOLLOW-UP	667
Pancreas			
Gem+Erl ± Xel (GECA)	II	FOLLOW-UP	120
Esophageal			
CF ± Pmab (POWER) *	III	OPEN	4

* collaborative trial

TTD Contribution

Near future:

- MACRO2 study (phase II): CTC (mCRC treated with cetuximab+QT)
- SETICC study (phase II): Optimizing the selection of patients on the basis of a pharmacogenomic signature (TS-3'UTR and ERCC1-118. genetic polymorphisms
- RAS, BRAF, Pi3K, Epi/anphireguline, PTEN, EGFR amplification in Pmab treated patients in phase II studies:
  - PLANET: FOLFOX+Pmab vs FOLFIRI+Pmab (liver mt.)
  - FRAIL: Pmab >70 years suboptimal
  - SPECTRA: CPT-11+Pmab (failure CPT-11)

TTD Contribution

Future:

- VISNU study will screen 750 p previously untreated with mCRC according to CTC count and gene status (RAS, BRAF and PI3K).
  - In VISNU-1 (phase III): 350 p with ≥ 3 CTC, will be randomized to receive FOLFOX-6+ bevacizumab or FOLFOXIRI+ bevacizumab.
  - In VISNU-2 (phase II): 240 p with < 3 CTC and RAS WT will be randomized to receive FOLFIRI+ bevacizumab or cetuximab according to the status of BRAF and PI3K.
- ULTRA study (phase II): optimizing the selection of patients using ultra-selection technology with next generation high sensitivity genotyping of p with mCRC refractory to irinotecan without any mutation on KRAS, PIK3Ca, BRAF and NRAS genes detected with highly sensitive techniques.